PHARMACOLOGY THERAPEUTICS AND PRESCRIPTION WRITING

For Students and Practitioners

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DEDICATED TO

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Botanist, Pharmacognosist, Recipient of the Flueckiger, Hanbury and Remington Medals, Dean Emeritus of the Columbia University College of Pharmacy, and my first teacher in Materia Medica

PREFACE TO FIFTH EDITION

THE RAPID ADVANCES in the chemical and biological fields, and the growing preference for pure principles rather than crude drugs, have brought into use many new drugs and modifications of old remedies. Parenteral administration is used widely. Because of these and many other therapeutic advances the present edition has been completely rewritten.

Among the new remedies considered may be mentioned amino acids, the blood fractions, coagulants and anticoagulants, heparin, dicumarol, curare, snake venoms, analeptics, antihistamines, convulsants and anticonvulsants, folic acid, rutin, thiouracil and its derivatives, sulfonamides, penicillin, streptomycin, demerol, metopon, the cardiac glycosides, the antimalarials, the mercury diuretics, and the BAL treatment of poisoning by arsenic, gold and other substances.

Details are given of the modern treatment of shock, the anemias, malaria, syphilis and other conditions.

The space allotted to alcohol, tobacco, and marihuana does not reflect their use in therapeutics, but rather the physician's interest in their toxic and habituation possibilities. Such substances as carbon monoxide, carbon disulfide, the cyanides and lead have been discussed, not as remedies, but as serious poisons.

As in previous editions, our guide throughout has been the need of the physician who employs drugs in the treatment of sick patients.

New York City WALTER A. BASTEDO

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Part I

INTRODUCTION

"Medicine sometimes cures, it often relieves, it always consoles."

THE PHYSICIAN'S calling has arisen from the needs of the sick, a person who is ill desiring the services of some one who can help him to get well. If the sick man cannot be made *well*, he wants as much improvement in his health as possible, so that he may do things; for example, attend to his business, or at least get about. If his health cannot be improved, he wants his comfort promoted and his life prolonged. Thus the objects of the practice of medicine are: to prolong life, to secure comfort, to improve health, to promote recovery, or to cure.

The physician accomplishes these objects by doing something for his patients, *i. e.*, by treating them. Therefore his ability to treat his patients successfully is what constitutes his direct personal value for them, and is the ultimate *raison d'être* of the physician's calling. Hence the importance of a familiarity with the available means of treatment, *i. e.*, with *remedial* or *therapeutic measures*.

Therapeutics is the science of the use of remedial measures. When a physician orders a patient to bed, he employs a therapeutic measure. Also when he orders a cold bath, a cathartic, or the application of a mustard plaster; or when he applies a splint to a broken arm, or removes an inflamed appendix, or sits by the bed and calms a nervous patient.

Preventive medicine goes a step further than remedial medicine, in that it designs to prevent the appearance or spread of disease.

The main therapeutic and preventive measures may be grouped as follows:

1. *Hygienic*—those which have to do with cleanliness, disinfection, the prevention of the spread of contagion, ventilation, the selection of a patient's bedroom, care of bedding, clothing, etc.

2. *Mechanical*—the use of bandages, splints, ligatures, catheterization to empty the bladder, massage, gymnastics, etc.

3. *Operative*—the performance of surgical and obstetrical operations.

4. *Physical*—the use of physical agents: heat, cold, light, electricity, x-rays, radium, etc.

5. *Hydrotherapeutic*—the local use of water and its modifications: ice, cold water, hot water, and steam, in the form of baths, packs, douches, etc.

6. *Dietetic*—the modifications of diet for the sick.

7. *Suggestive* or *psychotherapeutic*—suggestion, hypnotism, mental buoying, etc. To reassure a patient who is fearing the worst, to encourage, to stimulate the energies and the will are therapeutic measures. Fundamental, in many instances, for therapeutic success are patience, sympathy and understanding.

8. *Psychiatric*—the ascertainment and assessment of hidden mental conflicts, the bringing to light of which may serve as "mental catharsis."

9. *Pharmacologic*—the use of drug remedies.

Materia Medica.—Drug remedies are known collectively as the "materia medica," or medical materials. The science which deals with the properties of drugs is called "materia medica."

In connection with drugs, there are several great fields of work, the most important being:

1. *Pharmacognosy*—the study of the physical properties of crude drugs. The *pharmacognosist* studies the methods by which drugs are collected, their appearance on the market, the characters by which they may be identified and their quality estimated, their adulterants in the whole and in the powdered state, etc.

2. *Pharmacy*—the art of preparing drugs for use. Manufacturing pharmacy is the art of manufacturing drugs into forms suitable for use in medicine. Dispensing pharmacy is the art of making up prescriptions. The *pharmacist* studies weights and measures, solubilities, incompatibilities, keeping qualities, chemical reactions, the extraction of active principles, the making of preparations, and their combination into prescriptions.

3. *Pharmaceutical chemistry*—the study of the chemistry of drugs and preparations of drugs.

4. *Pharmacology* (pharmacodynamics)—the study of the action of drugs. The *pharmacologist* studies the action of drugs on the tissues and structures of living things.

The practicing physician does not require a knowledge of pharmacognosy, and he needs only such knowledge of pharmacy as may prove helpful to him in prescribing the drugs he desires his patient to have. But his knowledge of pharmacology should be extensive.

Drugs are either (1) pure chemicals, such as sodium bicarbonate or potassium iodide; (2) mixed mineral products, such as petrolatum or ichthammol; or (3) certain animal or plant parts or products. Of animal nature or origin are musk, cantharides, epinephrine, lard, honey; and of plant nature or origin are herbs, barks, roots, leaves, fruits, seeds, resins, alkaloids, etc.

Crude drugs are the commercial forms of the natural animal or plant drugs as they are brought to the market. Their employment in medicine is due to the fact that they contain or yield more or less definite chemical bodies of medicinal value, known as the "active constituents." In some cases these constituents are found in all parts of a plant, so that the whole plant is marketed as the crude drug; but mostly they occur in one part only, such as the leaf or root, or are stored in greatest abundance in one part, so that that part is selected for the market and is the crude drug. Sometimes, as in the case of asafetida, an exudate contains the active constituents and is the crude drug, no structural part of the plant being marketed at all. The crude drug of digitalis is the dry leaf; the crude drug of rhubarb is the dried root; of peppermint, the leaves and flowering tops; of cascara, the bark; of opium, the dried milk juice; of cantharis, the whole dried insect.

THE CONSTITUENTS OF ORGANIC DRUGS

These may be classified into: (1) the active constituents; (2) the inert constituents.

Inert constituents are the cellulose, wood, and other structural parts of the drug, and in some instances starch, albumin, fat, wax, coloring matter, and other substances which have no distinct pharmacologic action, though their presence in a preparation may have a modifying effect on the absorbability and activity of the active pharmacologic constituents.

ACTIVE CONSTITUENTS

The *active constituents* may be active in two different ways, viz.: *pharmacologically active, i. e.*, having an action on living organisms or tissues, and *pharmaceutically active, i. e.*, capable of causing precipitation or otherwise notable chemical changes in a prescription or preparation. Both kinds are found in cinchona bark, which contains not only quinine and other alkaloids upon which its pharmacologic activity depends, but also tannic acid, an astringent drug. In an ordinary dose of cinchona the tannic acid is too little in amount to have any important astringent effect, and is, therefore, not pharmacologically active; yet if the cinchona preparation is mixed with a preparation of iron, the tannic acid becomes pharmaceutically active and changes the iron salt into ink. Again, the pharmacologically active principles of digitalis are not readily soluble in water; so an aqueous preparation, such as the infusion, would not represent the activity of digitalis were it not for the fact that digitalis also contains a body which possesses the peculiar property of rendering the active medicinal principles soluble in water. This body (digitonin) is, therefore, pharmaceutically active, and as such is important.

A constituent is called an *active principle* when to it may be attributed, wholly or in part, the physiologic action of the drug.

The *active constituents* of organic drugs may be either:

(*a*) Single chemical bodies, or—

(*b*) Mixtures of such a nature that separation into their components is not advantageous.

The classes of active constituents are:

(*A*) *The Single Chemicals.*

1. Plant acids and their salts.
2. Alkaloids.
3. Neutral principles.
4. Toxalbumins.
5. Enzymes.
6. Hormones.
7. Vitamins.
8. Sugars, starches, and gums.
9. Tannins.

(*B*) *The Mixtures.*

1. Fixed oils, fats, and waxes.
2. Volatile oils.
3. Resins.
4. Oleoresins.
5. Gum-resins.
6. Balsams.

The last three are natural exudations from plants.

Plant Acids and Their Salts

The citric acid of lemons, the tartaric acid of grapes, benzoic, cinnamic, salicylic, tannic acid, and some of their salts are of interest pharmacologically. *Glycyrrhizin*, the sweet principle of glycyrrhiza (licorice), is really glycyrrhizic acid, and is sweet to the taste only in the form of alkaline salts. It is precipitated and rendered tasteless by acids.

Alkaloids

These are a class of organic bodies of alkaline reaction, composed of carbon, hydrogen, and nitrogen, and sometimes other elements. The class includes a great many of our most powerful drugs. Their basic or alkaline nature gives the name alkaloid (*alkali* and *eidos*, resembling). They possess the power of neutralizing acids with the formation of salts, and in doing so take up the acid without the liberation of hydrogen. In this respect they resemble ammonia, and differ from the alkali metals.

$$Na + HCl \rightarrow NaCl + H$$
$$NH_3 + HCl \rightarrow NH_3.HCl$$
$$C_{21}H_{22}N_2O_2 \text{ (strychnine)} + HCl \rightarrow C_{21}H_{22}N_2O_2.HCl$$

Some of the alkaloids are strongly basic, while others, such as caffeine, are so feebly basic that they are with difficulty made to form salts at all. Most are monacid, uniting one molecule of the alkaloid for each basic hydrogen in the acid. A few are diacid. Quinine forms two different salts with acid, those with sulfuric acid, for example, being *quinine sulfate*, the neutral sulfate, in which two molecules of quinine unite with one molecule of the dibasic sulfuric acid $(C_{20}H_{24}N_2O_2)_2.H_2SO_4 + 7H_2O$, and *quinine bisulfate*, the acid sulfate, in which only one molecule of quinine unites with each molecule of sulfuric acid, $C_{20}H_{24}N_2O_2.H_2SO_4 + 7H_2O$. The uncombined alkaloids, to distinguish them from the "alkaloidal salts," are known as "pure alkaloids," and are employed only when desired in oily solution.

Nomenclature.—To distinguish these basic substances from the neutral principles, the United States Pharmacopoeia makes all the names of alkaloids end in *ine* (Latin, *ina*), as quinine (quinina), cocaine (cocaina); and the names of the neutral principles end in *in* (Latin, *inum*), as aloin, chrysarobin and strophanthin. This is a simple device for distinction, and it serves a good purpose. The old form, ending in *ia*, as quinia, morphia, strychnia, is now obsolete.

Solubility.—The *pure alkaloids* are, as a rule, not readily soluble in water, but they dissolve more or less readily in alcohol, ether, chloroform, and the fixed and volatile oils. The *alkoloidal salts*, on the contrary, are mostly quite soluble in water, and fairly so in alcohol, but dissolve with difficulty in ether, chloroform, and the oils. For example, *atropine*, the pure alkaloid, is soluble in 455 parts of water, 2 of alcohol, 1 of chloroform, and 25 of ether; while *atropine sulfate*, the salt in common use, is soluble in 0.38 part of water (less than its own weight), in 5 parts of alcohol, in 420 parts of chloroform, and in 3000 parts of ether. Commonly in practice we employ the salts only, but when a solution is to be made in oil, or chloroform, or ether, we must use the pure alkaloid.

Incompatibles.—Alkaloids have extensive chemical affinities, and there are many reagents which are used in the laboratory as tests or precipitants for them. As physicians, however, we need know only their common prescription incompatibles, *i. e.*, those substances which form precipitates with alkaloidal salts, and which we would be likely thoughtlessly to include in a prescription containing an alkaloidal salt. Such common prescription incompatibles are:

1. *Alkalis*, which combine with the acid radical and throw the less soluble pure alkaloid out of solution (some of the alkaloids are destroyed by strong alkalis).
2. *Tannic acid*, which forms the comparatively insoluble tannate.
3. *Iodine, iodides*, and *bromides*, which form the comparatively insoluble iodides and bromides, or double salts.
4. *Mercuric chloride*, which forms insoluble double salts.

In these cases it must be borne in mind that the alkaloid is merely rendered less soluble in water, so if a large volume of water or a fair percentage of alcohol is present, the precipitation may not occur.

Physical Character.—Most of the alkaloids are solids, as morphine, quinine, and strychnine. A few of them are volatile liquids, as nicotine, pilocarpine, coniine, and lobeline, but these latter mostly form nonvolatile solid salts, which can be readily handled. Some are crystalline, some amorphous. Some of the salts are *deliquescent* and liquefy in moist air, as pilocarpine hydrochloride; others are *efflorescent* and lose weight in dry air, as the sulfate of strychnine and the sulfate of quinine. Some are decomposed by the heat of boiling water; others can stand much higher temperatures. Cocaine is decomposed at about 98° C. (*just below the boiling point of water*), and *its solutions* cannot, therefore, be sterilized safely by boiling. Some which will stand a higher temperature for a short time are: aconitine, atropine, brucine, cevadine, codeine, hyoscine, morphine, narcotine and strychnine; so that aqueous or alcoholic liquids containing these alkaloids may be brought to the boiling point, though not boiled for any length of time.

Taste.—The taste of alkaloids is bitter—that of strychnine and quinine intensely so; that of morphine, codeine, and caffeine mildly so.

Occurrence.—Alkaloids occur almost wholly in the higher plants—the dicotyledons. A few are found in the lower plants, and one of these, muscarine, is the poisonous principle in a few of the poisonous mushrooms. Some plants furnish many alkaloids, opium, for example, yielding about nineteen, and cinchona about thirty-two. In some cases one alkaloid is found in one part of the plant and another in a wholly different part of the same plant; often several are found together. Where a number of alkaloids occur in one plant they are usually closely related, both chemically and pharmacologically, as in the case of the alkaloids of belladonna; but in some instances they are quite different, and may even be pharmacologically antagonistic, as physostigmine and calabarine in the Calabar bean.

It is of interest that some alkaloids are confined entirely to one botanical family, as atropine, which is not found outside of the potato family (*Solanaceae*); or to one plant genus, as pilocarpine; or to a particular species, as morphine in the oriental poppy, and even then, perhaps, only when it is grown in a particular region. Others, however, are of wider distribution, as caffeine, which is found in various parts of the world in wholly unrelated plants, and berberine, found in the barberry, hydrastis, and moonseed.

The amount of alkaloid present in different specimens of a drug may vary within wide limits, as might be expected in plants growing under such different conditions of soil, climate, and weather, and

subjected to different methods of collecting, drying, preserving, etc. Yet the best quality of most drugs is notably uniform in its alkaloidal content.

Alkaloids are also produced by animals, for example, epinephrine; and poisoning from decomposing foods may closely resemble poisoning by plant alkaloids. Certain of the alkaloids, as choline, neurine and xanthine, are produced by both plants and animals.

Absorption.—Travell (1940) reports alkaloidal salts readily absorbed from an alkaline medium and not absorbed at all from an acid medium like the gastric contents. Absorption from the stomach is rapid if the contents are rendered neutral or slightly alkaline.

Artificial Alkaloids.—A number of alkaloids can be prepared artificially, and *theophylline,* which occurs naturally in minute quantity in tea leaves, was the first to be produced synthetically on a commercial scale. Other manufactured substances with alkaloidal properties are: *apomorphine,* prepared from morphine; *cotarnine,* prepared by hydrolyzing narcotine; *homatropine,* which results from the action of mandelic acid upon tropine, the mother substance of atropine; and *hydrastinine,* obtained by the oxidation of hydrastine. Three other artificial substances of the Pharmacopoeia, *hexamethylenamine, aminopyrine,* and *antipyrine,* have close chemical affiliations with the alkaloid group.

Neutral Principles

Besides acid and basic substances, plants furnish a large number of proximate principles which are chemically neutral. Their names end in *in* (Latin, *inum*), in accordance with the pharmacopoeial rule to distinguish them from alkaloids, as stated before. The most important are the *glycosides* (glucosides).

Glycosides.—The glycosides are a class of bodies which, under the influence of certain agents, decompose and yield some form of sugar, together with one or more other bodies. These decomposing agents may be heat, dilute acids, strong alkalis, enzymes, bacteria, or fungi. Most of the glycosides yield glucose; a few of them yield other sugars. Chemically, they are a loose group, and beyond their readiness of decomposition and their power to yield sugar, have no essential characters in common. They follow no rules as to solubility, or taste, or importance, some of them being bitter, some not; some soluble in water or alcohol, some not; some inert pharmacologically, and others, such as the active principles of digitalis, strophanthus, and cascara, being among our most valued remedies. The glycosidal nature of these bodies may be readily shown, for if they are warmed with dilute hydrochloric acid, the mixture will give the glucose test with Fehling's solution. Their ready decomposition indicates that preparations of drugs such as digitalis, which depend upon glycosides for their

activity, must neither be mixed with strong alkalis or acids nor subjected to continued heat.

There are two glycosides, *amygdalin* and *sinigrin*, which are practically inert pharmacologically, but are of importance because of the products of their decomposition by certain enzymes.

Amygdalin, with its particular enzyme, *emulsin,* occurs in bitter almonds, peach-pits, wild-cherry bark, and cherry-laurel leaves. In the presence of water the enzyme emulsin acts upon the amygdalin, causing it to split up into glucose, hydrocyanic acid (prussic acid) and benzaldehyde. The mixture of the two latter constitutes the highly poisonous volatile "oil of bitter almond." The amygdalin

$$\underset{\text{Amygdalin.}}{C_{20}H_{27}NO_{11}.3H_2O} + \underset{\text{Water.}}{2H_2O} \rightarrow \underset{\text{Glucose.}}{2C_6H_{12}O_6} + \underset{\text{Prussic acid.}}{HCN} + \underset{\text{Benzaldehyde.}}{C_6H_5COH} + 3H_2O$$

occurs in bitter almond to the extent of 1.75 to 3 per cent, so that one ounce of bitter almonds would be a poisonous dose.

Sinigrin, with its peculiar enzyme, *myrosin,* occurs in black mustard seed, and to some extent in horseradish root. Mustard flour, as purchased, contains nothing irritating, and has the odor of ordinary flour; but as soon as it is mixed with water, it develops the odor and irritant properties characteristic of mustard. This is because, in the presence of water, the myrosin acts upon the sinigrin and splits it up to yield glucose, potassium bisulfate, and allyl isothiocyanate, the last-named substance being the highly irritating "volatile oil of mustard."

$$\underset{\text{Sinigrin.}}{C_{10}H_{16}NS_2O_{10}K} \rightarrow \underset{\text{Glucose.}}{C_6H_{12}O_6} + \underset{\text{Potassium bisulfate.}}{KHSO_4} + \underset{\text{Allyl isothiocyanate.}}{C_3H_5CNS}$$

As this enzyme is rendered inert by a temperature above 60° C. (140° F.), very *hot water should not be used in preparing a mustard poultice or a mustard foot bath.* It is of interest that this volatile oil of mustard, when shaken with alcohol and ammonia water, deposits more than its own weight of crystals of *thiosinamine,* a drug which has been used by injection for the removal of excessive scar tissue.

Phlorhizin (*phloridzin* or *phlorizin*) is a glycoside obtained from the bark of apple, pear, cherry and plum trees, especially the bark of the root. It is nearly insoluble in cold water, but readily soluble in alcohol and alkaline liquids. Its administration is followed by glycosuria without hyperglycemia, [illegible] in the kidneys by which the "se[illegible] sugar is lowered. Phlorhizin is [illegible] Loewi, being due to the prevention of the kidney reabsorption by the sugar of the urine. It has been used as a test of the functional power of the kidneys.

Non-glycosidal neutral principles of importance in medicine are santonin, aloin, chrysarobin, etc. Some of those whose chief charac-

teristic is bitterness, as quassin of quassia, and chamomillin of chamomile, are often spoken of as *bitter principles* or *amaroids.*

Toxalbumins or Toxins

Of this extensive class of poisonous compounds, probably protein, some occur in plants, some constitute the poisonous products of bacteria, and some are the poisonous agents in the venom of snakes, scorpions, the tarantula, the Gila monster, spiders, bees, and other poisonous animals.

It is characteristic of these substances that their poisonous symptoms come on only after a latent period, and that, in susceptible animals, a relative immunity to the poison may be established by the repeated administration of small doses. This immunity is specific, the immunity to one toxin conferring no protection from poisoning by another. *Ricin* occurs in the castor oil bean and is left behind in the extraction of the castor oil; but there have been some cases of poisoning from the ingestion of the whole seeds. The author has met with a case in New York. The symptoms are violent gastro-enteritis and collapse. *Amanita toxin,* which occurs in the death's head fungus, *Amanita phalloides,* is responsible for many cases of mushroom poisoning.

The Enzymes or Ferments

The enzymes are a class of bodies capable of instituting chemical changes without apparently entering into the reaction or forming a part of the end-products. Their activity is very persistent, but not unlimited. They are unstable bodies, and are nearly all destroyed at a temperature of about 60° C. (140° F.). Examples are: *invertase,* which transforms cane sugar into fructose and glucose; *lactase,* which changes sugar of milk into glucose and galactose; *maltase,* which converts maltose into glucose; *emulsin* and *myrosin,* of whose reactions with certain glucosides we have spoken, and *pepsin, trypsin,* and the other enzymes of the digestive tract. A number of enzymes have a reversible action, *i. e.,* can, under certain circumstances, bring about changes just the reverse of the usual. The *oxidases* are concerned in the oxidation processes of the tissues.

Hormones

Hormones are chemical bodies that develop in specialized cells, notably those of the endocrine glands, and exert their effects on other glands or structures. Examples are epinephrine, insulin, thyroxin, estrone.

Vitamins

Vitamins are a group of substances not necessarily related chemically, that in minute amounts exert a profound influence upon, and

are requiste for, the nutritional and vital processes and the structural development of animals. They are present in various foods, and some have been made synthetically.

SUGARS, STARCHES, AND GUMS

These are carbohydrates of very slight pharmacologic action and of little importance as remedies, but of importance in dietetics and the arts. (See Part II.) *Manna*, derived from a tree of the ash family (*Fraxinus ornus*), contains the sugar, **mannite**, $C_6H_{14}O_6$, and is laxative.

Corn starch (amylum), $C_6H_{10}O_5$, is the starch in common use. It is employed as a dusting powder for the skin, or for pills to prevent their sticking together, or in the form of *starch water* as a soothing injection in irritative conditions of the lower bowel. To make starch water, the starch should first be hydrolyzed by mixing about a teaspoonful with 2 ounces of water, boiling until it forms a translucent paste, then diluting with water to ½ pint. Corn starch and arrowroot starch (*maranta*) are used as foods for children and invalids.

The **gums** are chemically closely related to the sugars and starches. There are two official, viz., *acacia*, which consists chiefly of arabinose, $C_{12}H_{22}O_{11}Ca$, and *tragacanth*, which contains bassorin. *Karaya gum* also contains bassorin, and is used as a bulk-producing laxative.

Acacia (gum arabic) is soluble in water and is demulcent. Its chief uses are pharmaceutical, as in the manufacture of mucilage and emulsions, and to give increased viscosity to mixtures containing heavy insoluble powders. It is also employed to give viscosity to saline liquids for intravenous infusion. (See Part II.) Its solutions ferment readily, turn sour, and become ropy; and it is precipitated from aqueous solution by alcohol.

Tragacanth does not dissolve in water, but swells up and makes an adhesive paste. Its active component is *bassorin*, which swells up in water and is used as a bulk-producing laxative.

Dextrin ($C_6H_{10}O_5$), known as British gum, is prepared from starch, being an intermediate stage in the change of starch to maltose or glucose. It is soluble in water, is sweetish to the taste and slightly laxative, and is the chief ingredient of some of the proprietary infant foods.

A *mucilage* is an adhesive, aqueous liquid or paste made from a gum. The official mucilages are those of acacia and tragacanth, both used for mechanical purposes.

TANNINS OR TANNIC ACIDS

These are a class of imperfectly defined astringent bodies of the aromatic group. They are all acids which form salts, and some of them are glycosidal in nature. They precipitate alkaloids, mercuric chloride,

and other salts of the heavy metals, and also proteins and gelatin. With iron compounds they make ink (blue to black in some cases, green in others), and with the connective tissue, protein, and gelatinous material of hides they make leather. This suggests the unwisdom of administering a gelatin-coated pill or capsule at the same time as a tannin-containing drug. They are freely but slowly soluble in water, and readily soluble in alcohol and glycerin. They occur mostly in the bark of trees, and in the plant-galls which result from punctures of insects. The various tannins are given the names of the plants which yield then, *e. g.*, that from cinchona is called "cinchotannin," or "cinchotannic acid," that from kino is "kinotannic acid," etc. The official "tannic acid" is quercitannin, and is derived from oak-galls. It is considered in Part II.

Fixed Oils, Fats, and Waxes

(*a*) The *fixed oils* and *fats* are mixtures of the three bodies, olein (liquid), palmitin (semi-solid), and stearin (solid), or close relatives of these, and in addition usually small amounts of other bodies. Olein, palmitin, and stearin are compounds of glyceryl, $C_3H_5\equiv$, with radicles of the various fatty acids. With alkalis they form soaps and glycerin. Castile soap, for example, is made by the action of sodium hydroxide on olive oil, which is nearly pure olein:

$$\underset{\text{Olein.}}{C_3H_5(C_{18}H_{33}O_2)_3} + \underset{\text{Sodium hydroxide.}}{3NAOH} \rightarrow \underset{\text{Castile soap.}}{3NaC_{18}H_{33}O_2} + \underset{\text{Glycerin.}}{C_3H_5(OH)_3}$$

The oils differ from the fats only in the relative proportions of these basal ingredients, the oils having more of the olein, which gives them a liquid consistence at ordinary temperatures, and the fats more of the stearin and palmitin, which make them solid or semisolid.

The fats and fixed oils have a greasy feeling, and are nonvolatile so that they leave a permanent grease spot. They cannot be distilled for they are decomposed by heat, with the generation of disagreeable acrid vapors (the familiar odor of burning grease). They are insoluble in water and alcohol (except castor oil and croton oil, which dissolve in alcohol), and are readily soluble in ether, chloroform, and benzine. They are almost all bland, nonirritating substances with nutrient and emollient properties; but on exposure to the air they gradually become rancid by the liberation of odorous and irritating fatty acids. Linseed oil (oleum lini), and to some extent castor oil (oleum ricini), if exposed to the air in thin layers, will dry like varnish, but most of the oils are of the nondrying type. A few of the fats and oils are of animal origin, *e. g.*, butter, lard (adeps), tallow, suet (sevum), and cod liver oil (oleum morrhuae); but the majority are of vegetable origin, as almond, cotton seed, cocoanut, corn, linseed, olive, peach

kernels, peanut and soy bean oils, and cocoa butter. The vegetable oils are found chiefly in seeds or in fruits. Lard readily becomes rancid and renders ointments granular and irritating. (See "Ointment Bases.") Cotton seed oil contains gummy and resinous constituents which make it inferior as a demulcent. When injected intramuscularly as vehicles for drugs, they form *oil tumors* of very slow absorption, though they may give up the contained drug to the tissues fairly rapidly.

Cocoa butter or *cacao butter* (oleum theobromatis) is obtained from chocolate seeds by compression between hot or cold plates. The fat is the cocoa butter, and the residue constitutes "cocoa." This fat has a very slight odor and taste of chocolate, is firm and rather brittle at ordinary temperatures, melts at the temperature of the body, and does not readily become rancid. It is used as a basis for the manufacture of suppositories, these retaining their shape at ordinary temperatures and quickly melting when inserted into a body orifice, such as the rectum. It is also used in massage.

Castor oil (oleum ricini) and *croton oil (oleum tiglii)* differ from the other fixed oils in being soluble in alcohol and in possessing special cathartic properties. (See Part II.) Castor oil is sometimes added to alcoholic hair lotions to prevent drying of the scalp (about 10 minims to a 3-ounce bottle).

Chaulmoogra oil is used in leprosy. Dose, 1 cc. (15 minims). The ethyl esters of its fatty acids, soluble in alcohol, constitute the pharmacopoeial *ethyl chaulmoograte*, which is employed by mouth or intramuscularly. Dose 2 cc. (30 minims). According to McCoy, former chief of the National Institute of Health, however, chaulmoogra is worthless in leprosy.

Glycerin (glycerinum) is a product of the saponification of fats or fixed oils. (See Reaction, page 11.) It is thick and viscid, has a sweet taste, mixes freely with water and alcohol, and has great affinity for water. It has extensive employment in pharmacy as a solvent, as a softening agent and preservative, and as a means for increasing the viscosity of liquids.

Action and Uses.—Applied in concentrated form to mucous membranes, it is astringent, causing the superficial cells to shrink by abstraction of water. For this reason it is used as an application to a relaxed uvula or pharynx. Diluted with water or rose water, as in "rose water and glycerin" (two parts to one) and in "calamine lotion" (see Zinc), it is used upon the skin as an emollient, serving to prevent the drying of the epithelium. With lemon juice or rose water it is also used as an application to the dry tongue of fever patients. In mixtures for internal use it serves as a sweetening agent and is slightly laxative. Given to a human being on an empty stomach it increases the sugar in the blood. (See also "Treatment by Rectum" under

Cathartics.) The *glycerites* are a class of official preparations in which glycerin is the solvent.

Soaps.—The soluble or detergent soaps are prepared by the action of an alkali upon a fat or oil, the potash soaps being soft, and those of soda being hard. They contain glycerin unless this is removed by washing, are soluble in alcohol and water, and have an alkaline reaction. Domestic soaps contain resin soap as well as fat soap, and washing soda or sodium silicate. Soap, especially green soap, with thorough scrubbing, is a good antiseptic for the bands and body. It is irritant locally and may be poisonous. Given intravenously it produces hemolysis and convulsions. Lewin reports two deaths from eating soap. (See also "Treatment by Rectum," under Cathartics.)

Hard soap (sapo durus) is prepared by the action of sodium hydroxide on olive oil. It is used in the manufacture of pills, soap liniment, chloroform liniment and saponified tooth powders. (For the chemical reaction see above, under "Fixed Oils and Fats.")

Soft soap or *green soap* (sapo mollis) is a potassium soap without the removal of the developed glycerin, and is employed extensively for cleansing the hands and skin preparatory to operative work. A liquefied form of it is the *liniment of soft soap* (linimentum saponis mollis), commonly called the "tincture of green soap," made by dissolving soft soap in alcohol and adding oil of lavender flowers.

Sulfonated petroleum soaps, the so-called "soapless soaps," are much used in industry. They have good wetting and foaming properties, which give them great cleansing power, and they are stable in hard water.

Lipoids or Fat Allies.—Those of interest to us are *lecithin* and *cholesterol*. *Lecithin* is a compound of glycerin and choline with stearic, palmitic and phosphoric acids, and is chemically a complex glycerophosphate. It can be saponified by alkalis. (See page 58.)

Cholesterol, a monatomic alcohol, $C_{26}H_{43}OH$, is a crystalline body found in all forms of protoplasm, but especially in brain tissue. It also occurs in abundance in the yolk of egg, in milk, cream, and butter, and in the bile. Gallstones are frequently the result of its precipitation in the bile ducts or gallbladder. The human body can probably synthesize all the cholesterol it needs. Quite probably it plays no rôle in therapeutics, except perhaps through irradiation. (See Vitamin D.)

Wool fat (adeps lanae), the purified fat of the wool of sheep, is made up of compounds of various fatty acids with isocholesterol. It is thus not a glyceryl fat, but a cholesterol fat, and is often classed with the waxes. It is yellowish white, of soft, sticky consistency, and, unlike the glyceryl fats, cannot be saponified by boiling with an aqueous solution of potash. Its greatest interest for us consists in its power to absorb more than its own weight of water, which makes it

of use as an ointment base for substances in aqueous solution. It is a secretion of the sebaceous type, not absorbable by the sheep's skin. Its mixture with 30 per cent of water is *hydrous wool fat* or *lanolin* (adeps lanae hydrosus).

The waxes are esters of the fatty acids with hydrocarbon radicles higher in the series than glyceryl. They are of firmer consistency than the fats, have a higher melting point, and cannot be saponified by boiling with an aqueous solution of potash.

Beeswax is from the honey bee, and is known in pharmacy as yellow wax (cera flava). When bleached it is called "white wax" (cera alba). It is chiefly myricyl palmitate, $C_{30}H_{61}.C_{16}H_{31}O_2$.

Spermaceti (cetaceum) is obtained from the head of the sperm whale, a single whale yielding many barrels. It consists chiefly of cetyl palmitate, $C_{16}H_{33}.C_{16}H_{31}O_2$. The best "cold creams" contain spermaceti and white wax; the poor ones are made of tallow.

The **ointments** or salves in common use are prepared mostly from wool fat and petrolatum, but also from lard, suet, white wax, yellow wax and spermaceti. See Skin Permeability, page 36.

Mineral Oils.—These are not constituents of vegetable or animal drugs, but for convenience may be considered with the other oils and fats. They are petroleum products, are mixtures of hydrocarbons, and are not subject to rancidity. The important medicinal petroleum preparations are:

Liquid petrolatum, U.S.P., (liquid paraffin, mineral oil) is a thicker and more oily liquid than kerosene. Its specific gravity is 0.860 to 0.905 at 25° C. and its viscosity 0.381 or over at 37.8° C. *Light liquid petrolatum, U.S.P.*, (petrolatum liquidum leve) has a viscosity of 0.37 or less, and specific gravity 0.828 to 0.880. Both are colorless, free from fluorescence, and practically tasteless, odorless, and unabsorbable from the alimentary tract. There are two types of mineral oil, the Russian, consisting mainly of unsaturated hydrocarbons, and the American, mainly saturated hydrocarbons, but more difficult to refine on account of the presence of sulfur bodies. Most of our supply is California oil, which more nearly resembles the Russian oils than other American oils.

Petrolatum, U.S.P., is of ointment consistency, is of yellowish color, and is without essential odor or taste. Decolorized it is *white petrolatum* (petrolatum album). *Hydrophilic Petrolatum, U.S.P.*, contains 73 per cent of white petrolatum, with cholesterol, stearyl alcohol, white wax and wool fat, and is miscible with water. *Liquid Petrolatum Emulsion, U.S.P.*, contains 50 per cent of liquid petrolatum, dose 30 cc. (1 ounce). *Paraffin* (paraffinum) is a white waxy solid, the purified residue after the liquid portion of the crude petroleum has been removed.

Petrolatum and white petrolatum have advantages in ointments

of good spreading and keeping qualities, but they are not absorbed through the skin. In intestinal or pancreatic fistulae, ointments made from petrolatum and paraffin, being nonsaponifiable, are efficient in protecting the skin from erosion; while the salves containing animal or vegetable fats become saponified by the alkaline secretions and are irritating. Used as a medium in nasal sprays liquid petrolatum slows or destroys the ciliary activity. It is in no sense antiseptic. (For the uses and limitations of liquid petrolatum internally see "Cathartics.") *Paraffin*, with added resorcinol, eucalyptol or other antiseptics is used to make a wax dressing for burns.

Kerosene, not official, is a limpid petroleum product from which the more volatile hydrocarbons are removed by distillation. It is employed as an enema in amebic colitis and for intestinal parasites. It is usually not absorbed from the intestines, but has caused poisoning.

Volatile Oils

These are the substances to which many plants owe their characteristic or essential odors. On this account they are often spoken of as "essential oils," or as the "essences" of plants.

They differ from the fixed oils in that—

(1) They are volatile, therefore can be distilled and do not leave a permanent grease stain. (2) They do not form soaps with alkalis. (3) They are soluble enough in water to impart to it their odor and taste. (4) They do not become rancid, but on exposure to light and air tend to oxidize and resinify.

They mix freely in any proportions with chloroform, ether, and the fixed oils, and are all soluble in absolute alcohol. Some, like oil of turpentine, require several times their own weight of official alcohol for complete solution. They are all mixtures, some of them quite complex.

Occurrence.—Most of them are found in plants, and each in a definite part of the plant from which it is derived, *e. g.*, oil of orange in the rind of the fruit; oil of cinnamon in the bark; oil of rose in the petals. From these parts they are obtained either by distillation or by means of a suitable solvent, such as benzine, which is afterward removed. Some of the delicate essential oils used in perfumery, as violet and heliotrope, are obtained by spreading the petals or flowers between wax plates, and afterwards separating the absorbed oil from the wax.

A few of the volatile oils do not exist in the living plant, and are formed either by the action of ferments on glycosides in the presence of water, as the oil of bitter almonds, or by destructive distillation. The latter are known as *empyreumatic* oils.

For convenience, the volatile oils preexisting in the plant may be grouped according to their nature, and those developed in the plant

part by artificial means may be grouped according to their method of production.

(*A*) Existing in plant as such:	1. Terpenes, C_xH_x (oils of turpentine, juniper, etc.);
	2. Terpenes + stearoptens (oils of lemon, peppermint, etc.).
(*B*) Not existing in plant as such, but developed from plant constituents:	3. From enzyme action (oils of mustard and bitter almond).
	4. Empyreumatic (oil of juniper tar, oil of tar, creosote).

Group 1.—Of all the volatile oils, the simple mixtures of terpenes are the least soluble in water and the most ready to resinify and deteriorate.

Group 2.—Of the mixtures of terpenes which are holding in solution one or more oxygenated bodies (of variable chemical nature, as aldehydes, ketones, ethers, acids, etc.), the terpene portion is known as the *eleopten,* and the oxygenated portion as the *stearopten.* The latter is usually solid, though sometimes liquid. It can be separated from the eleopten by cold (as the menthol of peppermint oil) or by fractional distillation. It is not always readily soluble in 95 per cent alcohol. Examples of stearoptens which are separated and used by themselves are camphor and menthol. It is to the stearopten that the characteristic odor of these oils is chiefly due, but the amount of stearopten present varies with the different oils. For example, the oils of orange or lemon contain only a small percentage of their peculiar stearopten and are nearly all eleopten, while the oils of wintergreen and birch are almost entirely composed of a liquid stearopten, which chemically is methyl salicylate. These oils are slightly soluble in water, and freely in alcohol, and, because of the stearopten, more agreeable in flavor, so they are largely used in the manufacture of the medicated waters and spirits. Some of them are heavier than water, as the oil of cinnamon.

Group 3 contains those oils which do not preexist in the living plant, but result from ferment action in the presence of water, such as the oil of bitter almond and the volatile oil of mustard (allyl isothiocyanate), not U.S.P.

Group 4 contains the empyreumatic oils, those which do not preexist in the plant, but result from its destructive distillation. U.S.P. are: *Juniper tar* (pix juniperi, oil of cade), and *pine tar* (pix pini). Both have a tarry odor, and are used for the treatment of chronic skin disease. *Pine tar ointment, U.S.P.,* contains 50 per cent of pine tar. The *syrup of pine tar, N.F.,* (syrupus picis pini), in dose of 10 cc. (2½ drachms), is used as an expectorant.

Coal Tar (pix carbonis), *U.S.P.,* from bituminous coal, is used in skin diseases. *Coal Tar Ointment, U.S.P.,* contains 5 per cent.

Creosote, N.F., is a mixture of phenols and phenol derivatives, chiefly

guaiacol and creosol, obtained during the distillation of wood tar, and has some of the properties of a volatile oil. *Creosote Carbonate, N.F.*, is a liquid without odor or taste, dose 1 Gm. (15 gr.).

The volatile oils have marked pharmacologic actions, but do not belong to a single pharmacologic group. Their actions will be considered in Part II.

Resins

Resins are all, or nearly all, mixtures of several different substances. They are an ill-defined group, forming amorphous masses which have a conchoidal shining fracture. They are insoluble in water and soluble in ether, chloroform, and the volatile oils. Many, but not all, of them are soluble in alcohol, and most of them dissolve in alkali with the formation of a nondetergent resin soap, which is miscible with water. Their composition is still a subject of study. Some of them, and perhaps all of them, are formed by the oxidation of volatile oils, in association with which in the plant they mostly occur.

Oleoresins

Oleoresins are the natural plant exudates which contain both volatile oil and resin. Balsam of copaiba, Canada balsam, and crude turpentine are examples, common rosin and oil of turpentine being the components of crude turpentine. (These natural oleoresins must be distinguished from the pharmaceutical oleoresins, which are artificial ethereal extracts of oily and resinous drugs, *i. e.*, extracts made with ether.)

Gum-Resins

Gum-resins are generally oleoresins in natural admixture with gum. They are obtained by the evaporation of the milky juices of certain plants. On rubbing a gum-resin with water the gum dissolves, and with the oil and resin forms a milky emulsion. Asafetida, myrrh and gamboge are examples.

Balsams

Balsams are resinous or oleoresinous exudates which contain benzoic or cinnamic acid, or both. These latter impart a "balsamic" odor. Benzoin, storax, balsam of Tolu, and balsam of Peru are official examples. Many fragrant substances are incorrectly called "balsam," *e. g.*, balsam of copaiba and Canada balsam, both of which are oleoresins. In some instances the resins, oleoresins, gum resins, and balsams are the only commercial representatives of their respective plants.

PHARMACEUTICAL PREPARATIONS

The chemicals and the various mineral, plant, or animal crude drugs may be employed in medicine as such without change, *e. g.*, sodium bicarbonate, cod liver oil, or powdered digitalis leaves; or

they may be made into pharmaceutical preparations, as the emulsion of cod liver oil, or the tincture of digitalis.

Pharmaceutical preparations are the prepared forms into which drugs are made for convenient employment in medicine. It is not convenient, for instance, to administer cascara in the form of cascara bark. It would be a disagreeable task for a patient to chew the bitter bark, but the fluidextract of cascara, a pharmaceutical preparation, represents the full physiologic activity of the drug, because the active principles are held in solution, and is easily administered.

In the preparation the drug or drugs—(*a*) may remain unchanged, as in the emulsion of cod liver oil, rhubarb pills, or powder of ipecac and opium; or (*b*) may be changed by chemical reaction, as in Fowler's solution of arsenic; or (*c*) may be made to yield their active constituents to a suitable solvent, as in preparations made by extraction. Preparations, too, may be employed in the manufacture of other preparations, as cinnamon water in making chalk mixture, and the extract of belladonna in making a belladonna plaster.

Extraction is the process of removing the active constituents of an animal or vegetable drug by means of a suitable solvent. By this process the inert woody fiber, cellulose, and other matters that are insoluble in the solvent employed are left behind, so that only the soluble matters of the crude drug appear in the preparation. In extraction the solvent is known as the **menstruum**, and this differs with the different drugs or types of preparation. It may be water, alcohol, alcohol and water, alcohol and glycerin, glycerin, wine, acetic acid, ether, chloroform, etc. Preparations made by extraction are:

(*a*) With aqueous solvent—some *extracts*, and *infusions* and *decoctions*.

(*b*) With alcoholic solvent (in most instances)—*extracts*, *fluidextracts*, and *tinctures*.

(*c*) With diluted acetic acid—*vinegars*.

(*d*) With ether—*oleoresins*.

Preparations made by extraction represent the activity of the crude drug, but in addition to the active principles, always contain more or less physiologically inert matter which has gone into the solution. Such inert matter is known as the "extractive," and it consists of such substances as fat, wax, oil, tannin, chlorophyll, etc.

Percentage Strength of Liquids.—The Pharmacopoeia lays down the rule that in prescriptions the term "per cent" has definite though different meanings in different circumstances. For solutions of *solids in liquids* the solids are weighed and the liquids measured, *e. g.*, a 4 per cent solution of cocaine hydrochloride is a solution of 4 Gm. of the salt in enough water (*q.s.*) to make a total of 100 cc. That is, 1 cc. would represent 0.04 Gm. of cocaine hydrochloride. For solutions of *liquids in liquids* all are measured, *e. g.*, a 10 per cent solution of oil of peppermint in alcohol is a solution of 10 cc. of oil of

peppermint in enough alcohol to make a total of 100 cc. For solutions of *gases in liquids*, the gas is weighed and the liquid measured, *e. g.*, ammonia water is a solution of 10 Gm. of ammonia gas in sufficient water to make the total 100 cc. These rules make calculation easy, because a given *measure* of a solution represents a definite amount of the dissolved ingredient.

To conform with the idea of weighing solids and measuring liquids the Pharmacopoeia specifies that in liquid preparations made by extraction a definite weight of the drug shall be employed in making a definite volume of the finished preparation. Hence these preparations have a definite relation in strength to the drug from which they are made, for the active ingredients of a definite weight of the drug are in the solution. The strengths of pharmaceutical preparations are indicated by the amount of drug used in their making, whether the drugs themselves are in the finished preparation or only their extracted constituents. Thus a measure of 100 cc. of the tincture of digitalis represents the medicinal activity of 10 Gm. of digitalis leaves; the tincture is, therefore, of 10 per cent strength. A measure of 100 cc. of the fluidextract of cascara represents the medicinal activity of 100 Gm. of cascara, hence the fluidextract is of 100 per cent strength.

Nomenclature.—The simple preparations are given simply the name of the drug prefixed by the name of the kind of preparation, as: syrup of ginger (syrupus zingiberis), tincture of digitalis (tinctura digitalis). The compound preparations have two types of nomenclature. If the active drugs are only two in number, or in some cases three, all are mentioned in the name, as: pills of aloes and iron (pilula aloes et ferri), elixir of the phosphates of iron, quinine, and strychnine (elixir ferri, quininae et strychninae phosphatum). If the important drugs are several in number, especially if one overshadows the others in importance, only one drug is named, and the name of the class of preparation is modified by the term *compound*. Examples are: compound tincture of gentian, which is made of gentian, cardamom seed and bitter orange peel; compound senna powder, which contains glycyrrhiza, senna, and sulfur.

DEFINITIONS OF THE KINDS OF PHARMACEUTICAL PREPARATIONS IN COMMON USE

Aqueous Liquids.—1. *Water* (Aqua).—A weak aqueous solution of one or more volatile substances (*e. g.*, peppermint or cinnamon water, chlorine water).

2. *Solution* (Liquor).—An aqueous solution of one or more non-volatile chemical substances (Fowler's solution).

3. *Mixture* (Mistura).—An aqueous liquid containing insoluble material (chalk mixture). It requires the label, "Shake before using."

4. *Syrup* (Syrupus).—A dense aqueous solution of sugar with or without medicinal or flavoring substances (syrup of ipecac).

5. *Mucilage* (Mucilago).—An adhesive aqueous liquid or paste made with gum (*liquid*—acacia; *paste*—tragacanth).

6. *Infusion* (Infusum).—A liquid obtained by steeping a vegetable drug in water and then straining. The water may be cold, warm, or hot, but the drug is not subjected to boiling. None are U.S.P.

7. *Decoction* (Decoctum).—A liquid made by boiling a vegetable drug with water, then straining. None are U.S.P.

8. *Juice* (Succus).—The juice expressed from parts of fresh plants ("fresh" meaning "undried"); an example is *limonis succus* (lemon juice). Alcohol may be added as a preservative.

9. *Injection* (Injectio).—A liquid prepared for parenteral administration.

Alcoholic Liquids.—1. *Fluidextract* (Fluidextractum).—An alcoholic or hydro-alcoholic liquid preparation made by extraction, and representing the drug volume for weight; *i. e.*, 1 cc. of the fluidextract represents the strength of 1 Gm. of the drug.

2. *Tincture* (Tinctura).—An alcoholic or hydro-alcoholic liquid preparation made by extraction and of a strength less than that of the drug; *i. e.*, tinctures are of the same nature as fluidextracts, but weaker. A few simple alcoholic solutions are incorrectly called "tinctures," *e. g.*, tincture of ferric chloride, tincture of iodine.

3. *Elixir* (Elixir).—A sweetened, aromatic, hydro-alcoholic liquid (aromatic elixir).

4. *Spirit* (Spiritus).—A simple solution of one or more volatile substances in alcohol (spirit of peppermint).

5. *Wine* (Vinum).—The wines are not now U. S. P. They are made like a tincture or solution, but with white wine and alcohol as the menstruum (bitter wine of iron).

Miscellaneous Liquids.—1. *Vinegar* (Acetum).—Made like a tincture, but with diluted acetic acid as the menstruum (vinegar of squill). None are U.S.P.

2. *Emulsion* (Emulsum).—A milklike preparation in which an oil is finely divided and its particles coated so that they will not run together again. Emulsions are: (*a*) *Natural*, as in egg yolk and milk. (*b*) *Gum resin*, as in emulsum asafoetidae; the drug contains gum, oil and resin, and on rubbing with water makes an emulsion. (*c*) *Artificial*, in which an adhesive must be added, as emulsion of cod liver oil.

3. *Honey* (Mel).—A liquid or semiliquid mixture of a drug with honey (honey of rose).

4. *Oleoresin* (Oleoresina).—A semiliquid ethereal extract of a drug which contains oil and resin. The oleoresin contains the ether-soluble constituents of the drug, the ether being evaporated off. It is of greater strength than the drug itself (oleoresin of male fern).

5. *Glycerite* (Glyceritum).—A liquid or semisolid solution in glycerin (glycerite of boroglycerin).

6. *Liniment* (Linimentum).—An oily or alcoholic solution or mixture to be applied to the skin (liniment of camphor).

7. *Lotion* (Lotio).—An aqueous liquid for local application (calamine lotion).

8. *Collodion* (Collodium).—A solution of a medicinal substance in collodion (cantharidal collodion).

9. *Nebula* (Nebula).—A spray for nose or throat.

10. *Oleovitamin* (oleovitamin).—An oil preparation containing fat soluble vitamins.

Solids and Semisolids.—1. *Extract* (Extractum).—A preparation of dry or plastic consistence, made by extracting a drug with a solvent, and then removing the solvent by evaporation. An extract is of greater strength than the crude drug. Most extracts are three to five times as strong as the drug from which they are made (extract of belladonna).

2. *Powder* (Pulvis).—A dry powdery mixture of drugs (compound chalk powder).

3. *Trituration* (Trituratio).—A powdery mixture of a drug with sugar of milk (*trituratio elaterini*, of 10 per cent strength). None are U.S.P.

4. *Mass* (Massa).—A plastic mixture for division into a number of equal objects, such as pills, troches, etc., and usually obtained by incorporating drugs with an adhesive substance (mass of ferrous carbonate).

5. *Pill* (Pilula).—A rounded or oval body of size to be readily swallowed, and made of cohesive drugs or drugs incorporated with an adhesive substance. Pills may be coated with sugar, gelatin, silver, keratin, or salol. The coating may be white, pink, chocolate colored, etc. (pills of ferrous carbonate).

6. *Troche* (Trochiscus).—A flat body, rounded or lozenge shaped, intended to be dissolved slowly in the mouth. It contains the medicinal substance, and in addition sugar, flavoring and adhesive material (troches of ammonium chloride).

7. *Compressed Tablet* (Tabella compressa).—A solid body made by the compression of a powdered drug or mixture of drugs in a suitable mold. With insoluble powders the hard compression retards disintegration. When the drug is readily affected by moisture, a dehydrating agent is added. Tablets may be sugar or gelatin coated to hide a bitter taste.

8. *Tablet Triturate* (Tabella triturata).—A solid body made of drugs triturated with sugar of milk. It disintegrates as the sugar of milk dissolves.

9. *Confection* (Confectio).—A pleasant tasting preparation made

by mixing medicinal powders and aromatics with syrup or honey (confection of senna).

10. *Granular Effervescent Salt* (Sal granulatus effervescens). —A preparation made by adding sodium bicarbonate and citric or tartaric acid to the drug, moistening with alcohol, and passing through a coarse sieve to form granules. It is added to water and drunk during or just after the effervescence (effervescent sodium phosphate).

11. *Paper* (Charta).—A sheet of paper impregnated with a medicinal substance (niter paper), or bearing it in a state of fine subdivision (mustard paper).

12. *Plaster* (Emplastrum).—A solid mixture which becomes plastic and adhesive on warming; it is spread in a thin layer over muslin, moleskin, etc., for application to the skin (emplastrum belladonnae).

13. *Poultice* (Cataplasma).—A soft, usually hot and moist paste for external application, as a flaxseed poultice.

14. *Ointment* (Unguentum).—A soft, fatty (unctuous) preparation which on rubbing melts at or about the temperature of the body (sulfur ointment).

15. *Cerate* (Ceratum).—An unctuous mixture of firmer consistency and higher melting point than an ointment (ceratum cantharidis).

16. *Oleate* (Oleatum).—A semisolid solution of metallic salts or alkaloids in oleic acid. It is for external use (oleatum hydrargyri).

17. *Suppository* (Suppositorium).—A solid which retains its shape at normal temperature, but readily fuses when inserted into a body orifice. Suppositories are usually made with a basis of cocoa butter and are: (*a*) *rectal*, cone shaped, weight 1 to 2 Gm. (15 to 30 gr.); (*b*) *urethral*, thin, pencil shaped, weight 2 to 4 Gm. (30 to 60 gr.); (*c*) *vaginal*, globular or elliptic, weight 4 Gm. (1 drachm). Urethral and vaginal suppositories are sometimes made of glycerinated gelatin. Small rectal suppositories used for children and in irritative conditions of the anus are made about 1 Gm. (15 gr.) in weight. Glycerin suppositories are made with sodium stearate.

18. *Enteric Coatings*.—These applied to capsules, pills or tablets, are designed to allow medicaments to pass through the stomach unliberated, but to be set free in the intestines within a reasonable time. The favorite enteric coatings of the past have been keratin and salol, but neither of these has proved reliable, and a thick coating of salol involves, in addition, the administration of sizable doses of this drug. At the present time stearic and related fatty acids, shellac, and wax combinations are employed.

The passage through the stomach and the site of disintegration are determined in animals by the manufacturer with x-rays of coated preparations of opaque or radio-active substances. Yet in humans they are far from perfect. The coating may prove ineffective in the stomach, or it may not dissolve quickly enough or at all in the intestinal tract. Therefore enteric coatings are unreliable.

TABLE OF METRIC DOSES WITH APPROXIMATE APOTHECARY EQUIVALENTS

The following *approximate* dose equivalents have been adopted by the Pharmacopoeia, National Formulary, and New and Nonofficial Remedies, 1946. They have the approval of the Federal Food and Drug Administration.

Liquid Measure

Metric	Approximate Apothecary Equivalents
1000 cc.	1 quart
750 cc.	1½ pints
500 cc.	1 pint
250 cc.	8 fluidounces
200 cc.	7 fluidounces
100 cc.	3½ fluidounces
50 cc.	1¾ fluidounces
30 cc.	1 fluidounce
15 cc.	4 fluidrachms
10 cc.	2½ fluidrachms
8 cc.	2 fluidrachms
5 cc.	1¼ fluidrachms
4 cc.	1 fluidrachm

Liquid Measure

Metric	Approximate Apothecary Equivalents
3 cc.	45 minims
2 cc.	30 minims
1 cc.	15 minims
0.75 cc.	12 minims
0.6 cc.	10 minims
0.5 cc.	8 minims
0.3 cc.	5 minims
0.25 cc.	4 minims
0.2 cc.	3 minims
0.1 cc.	1½ minims
0.06 cc.	1 minim
0.05 cc.	¾ minim
0.03 cc.	½ minim

Weight

Metric	Approximate Apothecary Equivalents
30 Gm.	1 ounce
15 Gm.	4 drachms
10 Gm.	2½ drachms
7.5 Gm.	2 drachms
6 Gm.	90 grains
5 Gm.	75 grains
4 Gm.	60 grains (1 drachm)
3 Gm.	45 grains
2 Gm.	30 grains (½ drachm)
1.5 Gm.	22 grains
1 Gm.	15 grains
0.75 Gm.	12 grains
0.6 Gm.	10 grains
0.5 Gm.	7½ grains
0.4 Gm.	6 grains
0.3 Gm.	5 grains
0.25 Gm.	4 grains
0.2 Gm.	3 grains
0.15 Gm.	2½ grains
0.12 Gm.	2 grains
0.1 Gm.	1½ grains
75 mg.	1¼ grains
60 mg.	1 grain
50 mg.	¾ grain

Weight

Metric	Approximate Apothecary Equivalents
40 mg.	⅔ grain
30 mg.	½ grain
25 mg	⅜ grain
20 mg.	⅓ grain
15 mg.	¼ grain
12 mg.	⅕ grain
10 mg.	⅙ grain
8 mg.	⅛ grain
6 mg.	1/10 grain
5 mg.	1/12 grain
4 mg.	1/15 grain
3 mg.	1/20 grain
2 mg.	1/30 grain
1.5 mg.	1/40 grain
1.2 mg.	1/50 grain
1 mg.	1/60 grain
0.8 mg.	1/80 grain
0.6 mg.	1/100 grain
0.5 mg.	1/120 grain
0.4 mg.	1/150 grain
0.3 mg.	1/200 grain
0.25 mg.	1/250 grain
0.2 mg.	1/300 grain
0.15 mg.	1/400 grain
0.12 mg.	1/500 grain
0.1 mg.	1/600 grain

Note—A cubic centimeter (cc.) is the approximate equivalent of a milliliter (ml.).

Noteworthy terms.

1 ounce avoirdupois	437.5	grains
1 ounce troy	480.0	grains
1 fluidounce of water (the standard of volume)	455.7	grains
1 pint of water weighs	7291.0	grains
1 pound avoirdupois is	7000.0	grains
1 pound troy is	5760.0	grains

1 minim of water weighs $\frac{455.7}{480}$ grains = 0.95 grains = 61.61 mg.

15 grains of water = 16 minims; 1 grain of water measures 1.05 minims = 0 0648 cc.

An imperial pint is 20 ounces; a United States pint is 16 ounces.

EXACT EQUIVALENTS OF METRIC AND APOTHECARIES' WEIGHTS AND MEASURES ACCORDING TO THE U. S. PHARMACOPOEIA

Volume.

1 cc.	16.23	minims
1 liter (1000 cc.)	33.8	oz.
1 minim (♏).	0.061	cc.
1 fluidrachm (ʒ)	3.696	cc.
1 fluidounce (℥)	29.57	cc.
1 pint (O)	473 18	cc.

Weight.

1 milligram, 0 001 (mg.)	0.0154	grain
1 centigram, 0.01 (cg.)	0.1543	grain
1 decigram, 0.1 (dg.)	1.543	grains
1 gram, 1.0 (Gm.)	15.4324	grains
30 grams, 30.0	462 9	grains
31 grams	478.4	grains
1 grain (gr.)	0.065	Gm.
10 grains	0.648	Gm.
15 grains	0.972	Gm.
1 scruple (℈)	1 296	Gm.
1 drachm (ʒ).	3.89	Gm.
1 ounce troy (℥)	31.1	Gm.
1 ounce avoirdupois	28.35	Gm.

ACTIVE PRINCIPLES AND ASSAY PROCESSES

As might be expected from the different conditions under which plants grow, the different methods of collecting, drying, and preserving drugs, the effects of age on the drug, etc., crude drugs vary in strength. On this account the use of active constituents by themselves has much to commend it, *e. g.*, quinine in preference to cinchona, strychnine in preference to nux vomica, resin of podophyllum in preference to podophyllum. These substances tend also to be more readily absorbed when thus separated from the extractive matter of the crude drug. But in many instances it is impossible or too expensive to isolate the active ingredients in pure form, or there is a preference for the combinations or mixtures as they occur in nature, so

pharmaceutical preparations, and even the powdered crude drugs, are much prescribed, even though their active principles are available.

This being the case, it is a matter of great importance that some of the more potent of these drugs and preparations are standardized by the Pharmacopoeia to contain a definite percentage of the active ingredients. For instance, when assayed by the process specified in the Pharmacopoeia, belladonna leaf must yield not less than 0.3 per cent of alkaloid; the tincture of opium, 0.95 to 1.05 per cent of morphine. These are known as *assayed* drugs or preparations.

An *assay process* is a process by which the strength of a substance or preparation is determined. There are three kinds of assay processes for drug preparations, viz., volumetric, gravimetric, and biologic. A biologic assay is a comparison by tests on animals of the strength of a substance with that of a standard having the same physiologic action. For digitalis, for example, the pharmacopoeial assay process ascertains the amount of the digitalis preparation that is lethal to cats, as compared with the standard.

THE PHARMACOPOEIA AND THE NATIONAL FORMULARY AND OTHER SAFEGUARDS OF THE SICK

In prescribing medicines it is of outstanding importance to the physician that any given title used in his prescription shall always call for the same substance, and that this shall have a definite potency, quality and purity.

Under the Federal Food, Drug and Cosmetic Act and corresponding acts in each state the titles and standards of the current edition of the United States Pharmacopoeia (U.S.P.), the National Formulary (N.F.), and the Homeopathic Pharmacopoeia, are legal or *official*. Thus when an official drug or preparation is called for in a prescription, the pharmacist is required by law to dispense material that conforms in strength, quality and purity with the official standard. Likewise, a manufacturer who labels medicines with an official title must have these conform with official standards, or must state on the label wherein they differ from the official standards. If a physician prescribes a preparation that is not official, the pharmacist may dispense one of arbitrary potency and made by any method convenient. Moreover, there may be in common use several different unofficial formulas that bear the same name.

The United States Pharmacopoeia (U.S.P.).—In 1820 a group of physicians, under the leadership of Dr. Lyman Spalding, met in convention and compiled the first United States Pharmacopoeia. Since then a convention of delegates has met every ten years to determine principles to govern revision of the work. The United States Pharmacopoeial Convention met last in 1940. It was composed

of several hundred delegates from the medical and pharmaceutical colleges, the State medical and pharmaceutical associations, the American Medical Association, the American Pharmaceutical Association, the Army, the Navy, the Public Health Service, and other bodies. It delegated the publication of the Pharmacopoeia and the business of the Convention to a Board of Trustees, and the work of revision to a *Revision Committee* of fifty persons distinguished for their contributions to biology, pharmacology, serology, therapeutics and clinical medicine, and to botany, pharmacognosy, inorganic chemistry, organic chemistry and practical pharmacy. Of this Revision Committee, a Sub-committee on Scope, which includes eighteen physicians, has had the duty of determining which substances and preparations should be admitted to the new Pharmacopoeia. It has based its selection primarily on therapeutic merit, but has taken into consideration also extent of use. Thus the titles of the Pharmacopoeia have been selected by a group of able physicians, from among the nonpatented and nonsecret remedies in common use, after prolonged and careful study and discussion of the therapeutic value of each remedy. The present Pharmacopoeia, known as "Revision XIII" became official on April 1, 1947. The initials U.S.P. on a label indicate the highest medicinal quality, the standards being enforced by the Food and Drug Administration.

The Revision Committee maintains Advisory Boards: An Anti-Anemia Products Board, a Vitamin Board, a Sterile Products Board, an Endocrine Board, a Blood Substitutes Board, an Insulin Committee, and Aminoacid, Penicillin, Streptomycin, and other special committees. It also standardizes and furnishes to research laboratories and manufacturers "Reference Standard" preparations of aconite, cod liver oil, digitalis, ergot, various hormones and vitamins, and other remedies.

There are a number of other national pharmacopoeias, the British, the German, the Swiss, the Japanese, the Mexican, etc. Cuba, Costa Rica, the Dominican Republic, Nicaragua, Panama, the Philippines, Ethiopia and Puerto Rico have adopted the United States Pharmacopoeia, which is published in a Spanish Edition.

The National Formulary (N.F.) is issued by the American Pharmaceutical Association. In contrast with the Pharmacopoeia its selections are based not on therapeutic merit but solely on extent of use. As its name implies it gives many formulas to facilitate prescribing. Because of their continued use, it admits many of the drugs and preparations that have been deleted from the Pharmacopoeia. It also gives stains, reagents and preparations for use in the clinical laboratory. The present revision, N.F. VIII, became official on April 1, 1947.

New and Nonofficial Remedies is a book compiled by the Council

on Pharmacy and Chemistry of the American Medical Association. It lists many of the more recently introduced drugs with a discussion of their merits. The decisions of the Council are based on thorough studies, but are not legal. *Useful Drugs,* also issued by the American Medical Association, is a selection for practice of U.S.P. and N.F. preparations and a number of recently introduced drugs. It presents a brief summary of the pharmacologic action, therapeutic uses and dosage. The Association also issues an *Epitome of the U.S.P. and N.F.*

Vaccines, serums, antitoxins and other biologicals, and the arsenicals used for syphilis are sold only under license from the National Institute of Health. New drugs are not allowed to be marketed until released by the Food and Drug Administration.

DOSAGE

The dosage is the amount estimated as necessary to produce the therapeutic effect desired. It must be less than would be likely to produce undesirable or toxic side actions. It may be one dose or several doses a day, as with most drugs; one or two doses a week, as with injectable liver preparations; or several doses close together, as with picrotoxin in barbiturate poisoning.

While most drugs have a wide range of effective dosage well below toxic amounts, there are others that to be effective must be given in amounts bordering on the toxic, for example, the arsphenamines, the sulfa drugs, gold salts, thiocyanates and most anthelmintics. The structures commonly damaged in toxic drug reactions are the skin, liver, kidneys, bone marrow and nervous system. The calculation of dosage involves the questions, not merely of how much to give, but also in what form the drug is to be administered, by what route, how often, and at what times.

The U. S. Pharmacopoeia gives the "Average Dose" of each therapeutic agent recognized by it. This is not the complete "dosage," but is the dose decided upon for adults as most likely to produce the therapeutic effect for which the substance is commonly employed, when given in the way commonly employed, that is, once a day, three times a day, and so forth. As a rule, the Pharmacopoeia does not specify the total dosage or how many of its doses are to be administered in a given time, but leaves these to the physician's judgment.

The *minimum dose* is the smallest capable of producing a medicinal effect. A *maximum dose* is the greatest dose that can be administered without probability of poisonous effects. A *toxic dose* is a poisonous dose.

Remedies are administered either in *single doses* or in *repeated doses.* A *single dose* of a medicine may be given *all at once,* as two compound cathartic pills or an ounce of whisky; or in *divided doses,*

to opium and other narcotics, and to strychnine, while, on the contrary, the child's dose of a cathartic or belladonna or arsenic approaches that of an adult. We have seen the same amount of belladonna given to a father and to his son six years of age with equal effect; and a child of three years not one whit more affected by a grain of calomel than was her mother by half the dose. On the other hand, we have seen a child of one year "doped" by 1/20 grain of powdered opium.

In old age the dose must be, as a rule, somewhat less than in the prime of life, and especially must skin irritants, irritant cathartics, narcotics and depressant drugs be used with caution.

3. Sex.—Women usually require smaller doses than men, not only because of their average smaller stature and quieter life, but also because of their greater susceptibility to any influences. During menstruation and pregnancy irritant cathartics, and during lactation saline cathartics, are to be avoided or used with caution.

4. *Temperament, Race, Occupation.*—The patient of highly neurotic temperament is more susceptible than the phlegmatic person. Such difference may be racial, the excitable Italian, for example, being more easily affected than the stolid Swede, or it may have to do with activity and occupation, the athlete or the man who works all day out-of-doors and is inured to hardship being less readily affected than the man of sedentary habits, the merchant, student, or artist.

5. Previous Habits (Toleration).—The morphine habitué can take with impunity a dose of morphine large enough to poison one not habituated, and will obtain no effect from the ordinary dose. An old toper with cirrhosis of the liver will fail to get a medicinal effect from the usual dose of a tablespoonful of whisky.

6. Susceptibility.—*Increased susceptibility* means lowered resistance, a condition in which the usual or expected effects are produced by less than the usual amounts. For example, 2 or 3 grains of quinine sulfate produce in some people the ringing in the ears, deafness and headache that in most persons do not come from less than [illegible]

usual. For example, some persons can take 2 or 3 cups of coffee and then sleep soundly, though this is enough to keep the average person wide awake for hours.

7. Idiosyncrasy or Allergy.—*Idiosyncrasy* is that condition in which a person develops special and unusual effects from a remedy, food or other substance ingested, which are not produced in most persons by any dosage. Some develop a rash after eating strawberries, others after eating lobster, fish or buckwheat. Sometimes all the members of a family show such an idiosyncrasy to some special

article of food, and it is manifest in successive generations. The same is true of drugs. A minute amount of cocaine dropped in the eye or applied to the nasal mucous membrane may cause dangerous symptoms in one patient, though cocaine is used in the eyes and noses of thousands of other patients without any untoward symptoms at all; or a dose of antipyrine may be followed by a marked rash, which recurs each time the drug is taken. These are unusual and unexpected effects, and depend not so much on the size of the dose as upon a specific and unusual reactivity of the patient to the drug.

Other examples of drug idiosyncrasy are: Atrophy of the liver from cinchophen, thrombocytopenic purpura from quinine and sedormid, collapse from aspirin, and agranulocytosis from aminopyrine, the arsphenamines and the sulfa drugs. *Drug rashes* are not uncommon from aminopyrine, antipyrine, arsenic, aspirin, barbiturates, bromides, chloral hydrate, cinchophen, gold salts, iodides, morphine, phenolphthalein, quinine, salicylates, the sulfa drugs and the serums. These reactions have no relation to the usual pharmacologic actions of the drug. For our protection, and the patient's, we might well cover the possibilities of idiosyncrasy and susceptibility in taking the personal and family history.

8. **The Nature of the Disease.**—In great pain, as in peritonitis, morphine may be borne in doses that would ordinarily be poisonous. On the other hand, in cyanosis or conditions with bad breathing, morphine should be used with caution because of its tendency to depress the respiration. Again, in Bright's disease or other conditions involving the eliminating organs, drugs may more readily accumulate in the system and cause cumulative poisoning; and in functional or organic disturbance of the liver certain substances, like phenol or morphine, may have a more pronounced poisonous effect than otherwise.

In barbiturate poisoning, strychnine and picrotoxin are employed in doses that ordinarily would be profoundly toxic. In the presence of glaucoma, atropine and other mydriatics, and, in pregnancy, irritating cathartics are to be avoided.

9. **The Object of the Medication.**—Quinine as a bitter appetizer may be given in doses of 1 or 2 grains, while quinine for malaria is given in a single large dose of 15 or 20 grains, followed by 5 grains three times a day for a month. In a cough mixture for a child syrup of ipecac is given in doses of 2 to 5 minims, but in croup, where an emetic effect is desired, a whole teaspoonful is administered.

It is to be noted that preparations for *local* action are active according to their percentage strength rather than according to the actual amount of drug employed.

10. **The Channel of Administration.**—Most drugs are absorbed from the stomach or duodenum with sufficient rapidity to give the

the fluid from running out, and the spot is gently massaged to promote diffusion of the liquid into the tissues. The hypodermic needle may be cleansed by first forcing water through it, and then allowing a few drops of alcohol to descend through it by capillarity. A fine wire drawn through the lumen keeps it permeable. (In the introduction of cocaine and similar drugs for local anesthesia where a local action only is desired, the needle is inserted just beneath the epidermis and gives a *superficial subcutaneous injection*, or an *intracutaneous injection*. This method is not used when a systemic effect is desired.)

There are certain advantages and disadvantages in hypodermic medication.

The *advantages* are: (1) *Definiteness of dose.* (2) *Rapidity of action.* (3) *Availability* when administration by mouth is not feasible, as when (*a*) the patient cannot swallow, as in unconsciousness, or (*b*) will not swallow, as in drunkenness or delirium, or when drugs are taken with suicidal intent, or (*c*) the alimentary tract is in a state of intolerance and nonabsorption, as in uncontrollable vomiting or diarrhea.

The *disadvantages* are seldom encountered. They are: (1) *Abscess formation*, either a sterile abscess from an irritant drug, or an infective abscess from unsterile solution, needle, or skin. (2) *Injection into a vein*, thus plunging the whole dose into the circulation at once, perhaps with disastrous results. As a rule, when the needle enters a vein, blood will ooze back into the syringe, in which case the needle is withdrawn and inserted elsewhere. (3) *Injection into a nerve*, with resulting great pain and even paralysis.

Hypodermic medication has a very restricted employment, because only those drugs whose dose in solution is of small bulk are available for this method of administration.

(*c*) **By hypodermoclysis,** in which a large quantity of liquid (500 to 1200 cc.) is injected into the loose tissues about the breasts or abdomen, or into the back below the scapula, or into the buttocks or thighs. The liquid is allowed to run in slowly by means of a funnel or reservoir and the rubber tube attachment to the needle. If the fluid is not isotonic, or nearly so, with the blood, or if it interferes by pressure with the circulation of the part, it may result in gangrene or abscess. The writer has seen extensive gangrene follow the injection of 200 cc. of 2 per cent solution of sodium carbonate.

(*d*) **By Rectum.**—Drugs may be placed in the rectum by means of an instillation, *i. e.*, a small injection, or in the form of a suppository or ointment. Absorption is often rapid, yet the uncertainty of absorption and the chance that the drug will be expelled limit the usefulness of this channel.

(*e*) **By the Skin, by Inunction,** in which an oily or fatty preparation is rubbed upon the skin and left to be absorbed. On account

of the uncertainty of absorption the dose may vary within wide limits. Mercurial ointment is so used in the treatment of syphilis.

(*f*) **By the Veins, Intravenous Medication.**—Drugs administered by a vein act with great promptness, the whole dose passing at once into the circulation. Intravenous medication may be by injection or by infusion. In *intravenous injection* the drug, dissolved in a small quantity of liquid, is injected from a syringe, or through a funnel and tube, the needle being plunged through the wall of the vein in a slanting direction and toward the heart. In *intravenous infusion* a large quantity of warm liquid, with or without the addition of drugs, is slowly passed into the vein through a vein needle. From intravenous medication the author has seen the following mishaps: hematoma from leakage of blood from the vein, extensive sloughing of the tissues from the lodgment of some of the drug outside the vein, thrombosis (in one case fatal from extension to the heart), local suppuration, and fatal pyemia. Larger doses than usual of some drugs, such as epinephrine, may be given if well diluted and administered very slowly. *Intra-arterial injections* of saline are sometimes employed.

(*g*) **Through the Lungs, by Inhalation**—of gas for absorption into the system, as in the use of chloroform or ether as a general anesthetic. (Inhalations of medicated vapors are employed also for a local effect on the respiratory organs.)

(*h*) **Intraperitoneally**, especially in children, for dextrose, neoarsphenamine, diphtheria antitoxin, etc.

(*i*) **Intraspinally**, as in spinal anesthesia.

(*j*) **Sublingually**, the drug being placed beneath the tongue.

(*k*) **By ion transfer (iontophoresis, electrophoresis)**, which, as defined by Dr. Richard Kovacs, is "the introduction of electrically charged particles into the skin or mucous membrane by the polarity effects of the galvanic current, whereby ions with a positive charge are introduced from the positive pole and ions with a negative charge are introduced from the negative pole." The Council on Pharmacy and Chemistry of the A. M. A. describes it as "Used to deposit on or in the tissues ions of certain salts and charged colloid particles from solution."

According to Kovacs, drugs administered by ion transfer are: (1) *Applied from the positive pole:* The metals, copper, silver, and zinc; vasodilating drugs, histamine and mecholyl; aconitine, cocaine, epinephrine, and calcium. (2) *Applied from the negative pole:* Chlorine, iodine and salicylic acid.

The Council reports benefit from the ion transfer of mecholyl, 0.2-0.5 per cent solution or histamine acid-phosphate, 0.1 per cent solution, in chronic ulcers, Raynaud's disease, scleroderma and certain vasospastic conditions of the extremities, and palliation in rheumatoid arthritis. Each treatment is restricted to a limited area. But the

Council directs attention to the following drawbacks: (1) Locally the ions may precipitate protein, causing chemical destruction of tissue. (2) The ions may be lost by reduction or oxidation to an inactive form, or by immediate precipitation as proteinates. (3) Because of high velocity the ions may be eliminated rapidly so that their concentration will be too low to be effective. (4) The treatment is costly.

OINTMENT BASES AND SKIN ABSORBABILITY

In the choice of an ointment or liniment base the object of the treatment must be borne in mind. It may be for a superficial effect to protect the epithelium from drying, to protect a denuded surface, or to medicate the epithelium. Or it may be for a deeper effect, to obtain absorption of an oil or fat intrinsically medicinal, as cod liver oil, to deliver contained medicaments for local action just beneath the skin, as cocaine, or to obtain the systemic effects of contained medicaments, as mercury ointment. As a rule, pure aqueous solutions are unabsorbable, though boric and salicylic acids are exceptions. Alcoholic solutions and volatile oils are readily absorbed. The ointment bases employed are made with fats and oils, oxycholesterols, waxes, ethanolamines and hydrophilic bases.

1. **Fats and Oils.**—These are greasy, and aside from a merely protective function, exhibit fair absorption along the hair follicles and ducts of the sebaceous glands (Eller and Wolff, 1939). They do not penetrate more than one-third the depth of the outer corneous layer (Harry, 1941), but in combination with wetting agents may penetrate as much as 4 mm. (Duemling). They may readily permit the absorption of dissolved ingredients. They are not absorbed by the sweat glands.

The evidence shows that fats and oils of animal origin (lard, lanolin, cod liver oil, goose-grease) give the best penetration, and next in rank are those of vegetable origin (cocoa butter, olive and other fixed oils); while those of mineral origin (liquid and solid petrolatum) are almost without power of penetration (Bliss, Eller and Wolff). Fats and oils promote the absorption of substances that dissolve in them, such as iodine, resorcinol, salicylic acid, methyl salicylate and other volatile oils, the oil-soluble vitamins, and the estrogens. MacBryde (1939) found estrogens in ointment form more active than when injected, but Eller's experiments showed little absorption. In fatty bases the bacteriostatic properties of ammoniated mercury, mercuric bichloride, yellow mercuric oxide and iodine are retained to a considerable degree, but not at all by phenol, zinc oxide, benzoic and boric acids (Gershenfeld, 1940, Foley and Lee, 1942). In general, a water-containing base is best for antiseptics (Harry).

Lard readily becomes rancid, but this action may be retarded by the addition of an antioxidant, such as cholesterol, guaiac or hydro-

quinone. *Petrolatum* has the advantage of not becoming rancid, and its low penetrating power may be increased by the addition of cholesterol bodies as lanolin or lecithin.

2. Oxycholesterols keep well, and do not dry out. *Wool fat* has great absorptive power for water through its content of iso- and oxy-cholesterols. With 30 per cent of water it constitutes *lanolin*, a yellowish, rather sticky base. This has moderate power of absorption through the skin.

3. The Waxes are spermaceti, white wax, yellow wax, glycerostearates, glycerolaurates, etc. They are not absorbed but form water-in-oil emulsions that to some extent allow absorption of medicaments dissolved in the water. Cold cream is made with white wax, spermaceti and rosewater.

4. **Ethanolamines, Alcohol and Glycerin.**—These are liquids that are miscible with water and favor absorption, the oleate and stearate of triethenolamine being used for vanishing creams. The U.S.P. recognizes triethanolamine, a thick fluid.

5. **Hydrophilic Ointment Bases.**—These can hold a large amount of water in which medicaments should be dissolved before admixture with the other ingredients. Hydrophilic ointments are not affected by ordinary variations of heat and cold, or by changes in pH, and can be washed off with water, but they do not remain stable indefinitely. *Hydrophilic Ointment, U.S.P.*, contains sodium laurylsulfate, glycerin, stearyl alcohol, 25 per cent of white petrolatum and 37 per cent of water. It should be kept in tight containers. *Hydrophilic Petrolatum, U.S.P.*, contains cholesterol, stearyl alcohol, white wax, 15 per cent of wool fat, and 73 per cent of white petrolatum, but no water.

Ointments are called *water-in-oil* when the water particles are surrounded by oil, their ingredients dissolved in water not being readily released. They are known as *oil-in-water* when the oil particles are surrounded by water from which the dissolved ingredients are easily liberated. They are miscible with water and removable by it.

In *ophthalmic ointments* insoluble solids must be in very fine powder and wetted with water. Because of the tear wetted structures they are best made with a water absorption base, such as hydrophilic ointment. Jellies are not good in the eye.

THE TIME OF ADMINISTRATION

This is of some importance, *e. g.*, the saline *cathartics* act most rapidly after a period of fasting, so are usually administered before breakfast. *Irritant drugs*, as arsenic or iron or digitalis, are best given after meals, when they become well diluted with the stomach contents, and come very little in contact with the stomach wall to irritate it. Quinine sulfate is given after meals not only because it is

irritant, but so that it may be dissolved by the acid gastric juice; otherwise its absorption is retarded or may not take place at all. Sleep producers are most effective at the natural time of sleeping, and when the surroundings are favorable to sleep; they may have no effect at all if the patient is up and about. Sodium bicarbonate given on an empty stomach, *i. e.*, before a meal, is absorbed as sodium bicarbonate, and furnishes alkali directly to the blood; but if it is given during the digestive period, it neutralizes the hydrochloric acid of the gastric juice, is changed to sodium chloride, and sets free carbon dioxide. Appetizers must be given just preceding the meal, and are useless otherwise.

SITES AND MODES OF ACTION OF DRUGS

Drugs may be employed to act as such:

1. *Independently of the human body,* as antiseptics on microorganisms in disinfection.

2. *In or about the human body, but not on its structures,* as in the destruction of a tapeworm, skin parasites, etc., or as in the neutralization of a hyperacid gastric juice by an alkali.

3. *On the structures of the human body.* Drugs may act on the tissues —(*a*) *through their physical or mechanical properties,* as when cold cream is applied to a chapped face to soften the epithelium and prevent its drying; or when bismuth subnitrate, given for diarrhea, coats the mucous membrane of the bowel and soothes and protects it. Or they may act (*b*) *by their chemical affinity* for one or other constituent of protoplasm, so that either the functional power of the cell or the actual cell structure is changed. Some of these are *general* in their action, affecting practically all forms of protoplasm (though not all forms to a like degree), and when the action of these drugs is powerful, they are known as *general protoplasm poisons.* Such are alcohol, chloral hydrate and quinine. Other drugs are *selective,* exerting their influence only on special groups of cells and having no effect upon the vast majority of body structures. This is presumably owing to a chemical affinity for some component of the cell. Such drugs are strychnine, which has a selective affinity for certain portions of the central nervous system, and pilocarpine, which has an affinity for secretory nerve endings.

The effect of drugs on cells is to stimulate them, to depress them, or to change and destroy them. *Stimulation* is an effect on cells by which their power or their readiness to function is increased. *Depression* is an effect on cells by which their power or readiness to function is lessened. *Paralysis* is the cessation of the power to function.

Irritation implies an anatomical rather than a functional effect, tending toward the harmful. It has to do with actual changes in the

cell structure. In its mild degrees irritation may have the effect of stimulation; in stronger forms irritation may overwhelm the cells and have the effect of depression; while excessive or continued irritation induces inflammation and even actual death of the cells involved.

By exhaustion from overwork, continued stimulation may result in depression or even complete cessation of the work of the cells; but this is a functional inactivity from fatigue, and a period of rest and nutrition will usually restore the cells' power.

Often a drug will be found to stimulate one structure and depress another, as atropine, which stimulates the vagus center and depresses the vagus endings; or pilocarpine, which stimulates the nerve endings in the sweat glands and tends to depress heart muscle.

POTENTIATION, SYNERGISM, AND ANTAGONISM

Potentiation is the increase in activity of a drug by the administration of another drug. *Synergism* is the production by two or more like drugs of effects beyond the sum of the effects of the individual drugs. *Antagonism* is the opposition of one drug to another.

As might be surmised, the same dose of a drug will exert its usual form of activity more easily if given with other drugs of the same class; and a combination of two similar drugs may gain a result that one alone will not give in any dose.

On the contrary, a drug may lose part or all of its power because of some agent that has the opposite physiologic effect. An antagonist may act—(*a*) *on the same structures*—for example, bromides prevent the convulsions of strychnine, both acting on the spinal cord; pilocarpine stimulates the vagus nerve endings, which are depressed by atropine; (*b*) *on different structures*—for instance, digitalis slows the heart by stimulating the vagus center, while atropine prevents this effect by depressing the vagus nerve endings; epinephrine stimulates the nerve endings in arterial muscle, causing contraction of the arteries, and this effect can be wholly neutralized by nitroglycerin, which depresses the arterial muscle itself.

Incompatibility should not be confused with antagonism. It is a pharmaceutical term, and should be confined to prescriptions. Incompatibility may be said to exist between two substances when their admixture in a prescription results in chemical or physical change (other than mere solution). (See Chapter on Prescriptions.)

SCIENTIFIC AND EMPIRIC THERAPEUTICS—ANIMAL EXPERIMENTATION

The use of drugs without an adequate scientific explanation of their effectiveness is *empiric*. Most of our drugs have come into use empiri-

cally, *e. g.*, digitalis in heart disease, mercury in syphilis, quinine in malaria, and colchicum in gout. But because of scientific experimentation, largely by the use of animals, the actions of many of these can now be explained.

The *pharmacologist* furnishes invaluable information about the physiologic and toxic possiblilities and limitations of a drug. For the most part, he experiments with normal healthy adult domesticated animals and turtles, frogs, etc., properly fed, cared for and protected, and living a regular and uneventful life without the anxieties of the struggle for existence; and many times he employs toxic intravenous doses. For experimental purposes, he may induce disease in an animal but, as he well recognizes, it is seldom like the disease in humans that it is designed to resemble.

The *physician* deals with human beings at all stages from birth to senility, animals of highly developed psychic nature, frequently harassed by the trials and difficulties of human existence, living in all sorts of conditions and varied climates, improperly fed, undernourished or overnourished, and victims of bad habits, inherited weaknesses, dangerous exposures, chronically diseased organs, injuries or acute illnesses. It is not the physician's function to prescribe drugs for normal people.

Thus, for the best guidance in the use of remedies in practice, the observations and conclusions of the pharmacologist must be tested as to their practical value by extensive clinical use, and the necessarily grosser observations and conclusions of the clinician must be explained, checked and modified by the more detailed and more carefully controlled experiments of the pharmacologist.

In this way we make progress in therapeutics, and thereby contribute to the comfort, happiness, and efficiency of human beings. Indeed, physicians in treating human beings and veterinarians in treating domestic animals and pets could accomplish but little in comparison, were it not for knowledge gained by animal experimentation. In addition, we owe to experiments on animals much of our knowledge of the body activities, conditions in disease, the development of immunity and many other important truths concerning disease, so that the obligations of the human race to animal experimentation are enormous.

Yet in spite of these facts, there is a continual effort by a number of people to abolish vivisection or, if that is impossible, so to restrict it that our physiologists, pharmacologists, bacteriologists and others who require animals for their investigations would be seriously hampered. It is by the medical profession that the laity must be educated to know how much inhumanity would result should the antivivisectionists succeed in their legislative efforts to stop the use of animals in experimentation.

THE SCOPE OF TREATMENT

Local treatment is that applied directly to the part to be affected. *Remote local treatment* is that in which a drug, after passing through the body, acts locally during its excretion, as methenamine in disinfecting the urine. *Systemic treatment* is to affect the structures of the body after absorption. *Specific treatment* is a direct attack upon the causative factors in disease, *e. g.*, quinine in malaria, arsphenamine in syphilis, and antitoxin in diphtheria. There are but few specific remedies known. *Replacement treatment* is the administration of a substance to make up for a deficiency of some physiological agent normal to the body, as insulin in diabetes. *Symptomatic treatment* is designed to combat the various symptoms as they arise. For example, in typhoid fever if there is constipation a laxative drug is administered; if there is diarrhea, a constipating drug; if the heart is weak, a cardiac stimulant; if the heart is strong it needs no drug at all.

Expectant treatment is a term applied to the administration of mild and harmless remedies while the development of symptoms is awaited. For example, if one sees a child with fever but cannot diagnosticate the disease at the first visit, one may prescribe solution of ammonium acetate, which satisfies the patient and the family, tends to do good, does no harm, and does not interfere with the later diagnosis of the disease. *Expectant treatment should not be employed if its necessity can be avoided.* A remedy employed in expectant treatment is known as a *placebo* ("I placate or please"), and in the selection of a placebo it is well to choose one with some fitness to the case in hand, as in the example above, so that the tendency will be good even though its power is slight. In neurotic conditions a placebo is sometimes administered for its psychic effect.

HOW MUCH SHALL WE LEARN ABOUT DRUGS?

The subject of the materia medica is an extensive one, and the textbooks contain many things that the physician does not need to know. He *need not learn* the pharmacopoeial definition, where and how a drug grows, the method of its collection, its physical and microscopical characters, its preparation for the market, its adulterants, the process of manufacture of chemical drugs, the shapes of crystals, melting points, etc. Such data are for the pharmacist, the chemist, and the pharmacognosist, the men upon whom the physician must depend for his proper supply of good drugs.

But as physicians we *need to know* the following:

1. **The English and Latin names of drugs** and their preparations. In prescriptions we choose to use either the English or the Latin names only, but in the literature find both the English and the Latin, so we must know both.

2. **The Active Constituents of Organic Drugs.**—Of particular importance are those active constituents which are isolated from the drug and used by themselves in medicine, as morphine, strychnine, salicin, menthol, etc., or those which make undesirable incompatibles, as tannic acid.

3. **The Solubilities and Incompatibilities** of chemical drugs and of active constituents, where these become of importance from a prescription or utility point of view.

4. **Preparations, with Their Strengths and Doses.**—These are the official preparations, and such unofficial ones as are in common use. The average dose is given in the Pharmacopoeia and the National Formulary, and this, in most instances, is the dose to learn; and since what is desired for the patient is a therapeutic dose of the drug itself, the dose of the preparation should be such an amount as will represent the desired dose of the drug. The learning of doses is greatly facilitated by the pharmacopoeial custom of having one strength for all the more powerful preparations of a given class. For example, all *fluidextracts* are of 100 per cent strength; therefore their dose is that of the drug, but in liquid measure, *i. e.*, each cubic centimeter is equivalent to 1 Gm. of the drug. All potent *tinctures* are of 10 per cent strength, so their dose is ten times that of the fluidextract. Most *extracts* approximate four times the strength of the drug, hence have a dose of one fourth as much. For preparations, therefore, the doses do not have to be carried in mind as separate things, but can be instantly calculated from the percentage strength if the dose of the drug itself is known. For example, the dose of digitalis is 0.1 Gm. (1½ gr.), therefore that of the **10** per cent tincture is 1 cc. (15 minims), and that of the 1.5 per cent infusion is 6 cc. (1½ drachms). These amounts of the specified preparations each represent the dose of 0.1 Gm. (1½ gr.) of digitalis.

5. **Pharmacologic Action.**—How the drug acts. This includes the expected or usual action and any unusual actions, from both therapeutic and toxic amounts.

6. **Toxicology.**—The symptoms and treatment in case of poisoning.

7. **Therapeutics.**—An extensive subject of immediate practical importance to every physician, to be studied in a general way with pharmacology, as in this book; but to be studied in greater detail in connection with the individual diseases. It is in therapeutics that there is so much of the traditional, the old-fashioned, the empiric; and the crying need of the medical profession is that, where possible, drug therapeutics shall be based directly upon thorough pharmacologic knowledge tried out by clinical tests.

8. **Administration.**—How best to prescribe or administer the remedy.

9. **Cautions and Contraindications.**—Conditions in which the drug is dangerous, or may be prescribed only with special caution. *Indication* is a term used in medicine for the kind of treatment "indicated" or "pointed out" by the symptoms or disease of the patient. We say, for example, that "the indications in such a sickness are that the patient shall remain in bed, on a milk diet, and shall have a dose of calomel." Or, to put it in another way, we say that "rest in bed, a milk diet, and calomel are indicated," *i. e.*, "pointed to" by the symptoms as the means of treatment to be employed. *Contraindication* has the opposite meaning; it is a condition in which the drug should not be employed.

THE PHARMACOLOGIC ACTION

In this extensive field almost any kind of "aide-memoire" will be of value. It will, therefore, be our general plan to take up in natural succession the actions of each drug as follows: first, its action independently of the body, then its local action, its absorption into the system, its systemic action, its elimination from or disposal by the body, and finally its action (remote local) as it is being excreted. Such a scheme in detail is illustrated in the following chart:

(*a*) **On micro-organisms nnd enzymes**—action away from the body, *e. g.*, antiseptic action.

(*b*) **Local action**—

1. *On skin and adjacent mucous membranes*—nose, throat, eye, vagina, rectum, urethra, bladder.
2. *On alimentary tract:*

   Mouth—taste, appetite, saliva, astringency.

   Stomach { on contents—acids, enzymes, food substances. / on wall—secretion, movements, absorption of food and drugs, pain—emetic, antemetic.

   Intestines—on contents, secretion, movements, pain, character of stools.

   Liver, pancreas—flow of bile, pancreatic juice, etc.

(*c*) **Absorption of drug** { at what points or not at all. / how rapidly.

(*d*) **Systemic action**—

1. *On the circulatory organs:*

   Blood—corpuscles, chemistry, coagulability.

   Heart—auricles and ventricles { rate—slower, faster. / force—weaker, stronger. / rhythm — regular or irregular.

Arteries—contracted or dilated.

Arterial pressure—higher or lower.

Always learn through what mechanisms, and how, an effect is brought about. It is not enough to know simply that the heart is faster or slower, or weaker or stronger.

2. *On the respiratory organs:*

   Movements { depth. rate.

   Bronchi—secretions, muscle.

   Cough—effect of drug depends on whether cough is due to excessive secretion, lack of secretion, or irritation of throat, pleura, etc.

3. *On the nervous system and sense organs:*

   Cerebrum—intellect, emotions, sleep, pain, motor area (motion, convulsions, paralysis).

   Cerebellum—equilibrium.

   Medullary and basal centers—vagus, vasoconstrictor, respiratory, heat-regulating, pupil-dilating, secretory, vomiting.

   Spinal cord—reflexes { muscle tone. convulsions, paralysis.

   Peripheral—sensory, motor, secretory.

   Senses—sight, hearing, smell, taste, touch.

   Eye { external—conjunctiva and cornea. internal,—pupil, accommodation, eyeball tension.

4. *On muscle and bone.*
5. *On metabolism and temperature.*
6. *On secreting glands.*
7. *On genital organs* { male. female—menstruation, pregnancy, labor, etc.

(*e*) **Elimination or disposal of drug** { how changed in body. where stored in body. elimination by what route and in what form. rapidly or slowly—cumulative.

(*f*) **Remote local action**—on excretory organs during elimination—by kidneys, bladder, urethra, skin, bowels, lungs, mammary glands; or in urine, milk, sweat, breath, etc.

(*g*) **After-effects.**

(*h*) **Untoward effects**—unexpected or unusual.

(*i*) **Tolerance**—habit formation.

Such a scheme as the above leads to completeness in the consideration of a drug's action.

(B) MECHANICAL APPLICATIONS

These are for local application, to act as protectives in a purely mechanical way. Such are *collodion* (an alcohol-ether solution of soluble gun cotton), *flexible collodion* (collodion + castor oil), *adhesive plaster, solution of sodium silicate* (liquid glass) and *plaster of paris* (dried calcium sulfate). The dusting powders, such as *starch, kaolin, fuller's earth, talcum,* and *lycopodium,* act both as protective and drying applications. Sollmann found the percentage of its own weight of water adsorbable to be for corn starch 80, for kaolin 73, for fuller's earth 70, for talcum powder 61. (See Adsorbents.)

SWEETENING AGENTS

These are glycerin, sugar, syrup, and saccharin. Except for the last they are discussed elsewhere.

SACCHARIN

Saccharin, U.S.P., gluside or benzosulfinide, $C_6H_4SO_2.CONH$, is an acid anhydride soluble in 290 parts of water and 31 of alcohol. *Saccharin sodium, U.S.P.*, is soluble in 1.5 parts of water and 50 of alcohol. Of the latter 60 mg. is equal in sweetening power to about 30 Gm. of sucrose, but it has a chemical acid sweet taste that is not so pleasing as that of sugar. As it is slightly antiseptic and is not fermentable, it has been much employed in chewing gum, chewing tobacco, ginger ale, soda water, and canned foods; but it is not a food and lacks the caloric value of the sugar for which it is substituted.

Mathews and McGuigan considered it a deterrent in digestion by ptyalin, pepsin, and trypsin, but Roger and Garnier found that the acid anhydride activated pepsin mildly in the same way as hydrochloric acid. Folin administered 0.15 to 1.75 Gm. ($2\frac{1}{2}$ to 27 gr.) daily for five months to young adults, and concluded that it "is not injurious to the health of normal sound adults." The Saccharin Committee of the Advisory Council of the New York Department of Health, of which the author was Chairman, failed to find evidence of action deleterious to health from any amounts that could possibly be taken as a sweetener of food. Mercier took 5 Gm. (75 gr.) a day for fourteen days without harm. Furthermore, the extensive use of the drug by diabetics and the obese has not brought to light any deleterious actions. The lethal dose for a rabbit is in excess of 10 Gm. ($2\frac{1}{2}$ drachms), and it is rapidly excreted by the kidneys in unchanged form. In medicine it is employed solely as a non-nutritive sweetening agent, as in diabetes, obesity, and some fermentative diarrheas.

Dulcin, said to be sweeter than saccharin, is paraphenetolcarbamide.

In the blood, owing to the influence of insulin, dextrose exists in an unstable form that readily undergoes oxidation in the body. Administered dextrose cannot be utilized if there is a dearth of insulin. A 5.4 per cent solution is isotonic with the blood.

Absorption.—*In the stomach* hypertonic solutions are readily absorbed, the rate of absorption increasing with the concentration (Abbott et al., 1938). Isotonic solutions are little absorbed, and dilution in the stomach is very little. *In the duodenum,* low concentrations are absorbed, but high concentrations are diluted to perhaps 5 per cent, to be absorbed in the jejunum and ileum (Shay, Gershon-Cohen et al., 1938 to 1941; Abbott et al., 1938).

Absorption by Rectum.—It is practically the consensus that dextrose, whether in isotonic or hypertonic solution, is not absorbed rapidly enough to affect the blood sugar figure. After 80 Gm. in 240 cc. Pressman obtained no rise in the blood sugar. After four hours he recovered 24 per cent of the dextrose from the rectum and there was evidence of much fermentation. Garrer et al. (1941) found the absorption rate in the rectum one-tenth of that in the small intestine, owing to the absence of phosphatase. After one to two hours they recovered much of the dextrose from the rectum. Moore and Burget, (1934), ascertained that small amounts of sodium chloride had no influence on absorption, but small amounts of sodium bicarbonate retarded it and resulted in a marked influx of fluid into the gut. On the other hand, in diabetics, Garbat and Jacobi, and also Curry, obtained a rise in the blood sugar, and Collins and Boas, from 25 Gm. of dextrose by rectum, secured immediate relief from hypoglycemic reactions. In colostomy patients, on placing dextrose in the colon, Curry noted rises in the respiratory quotient and heat production, though no rise in the blood sugar. Groen (1938) found decreased absorption of dextrose given by mouth, in the diarrheas accompanying gastro-intestinal disease. *Subcutaneously,* 20 Gm. took four and a half hours to produce even a slight rise in the blood sugar (Hopkins). It may therefore be said that *dextrose is absorbed readily when given by mouth, but not when given by rectum or subcutaneously. Intraperitoneally,* an isotonic solution is readily absorbed.

Intravenously, Woodyatt, Sansum and Wilder ascertained that in 10 to 50 per cent solution dextrose could be introduced at a rate of about 0.85 Gm. (12½ gr.) of dextrose per kilogram of body weight per hour without producing glycosuria or diuresis; *i. e.,* 63 Gm. per hour for a weight of 70 Kg. At a more rapid rate glycosuria and diuresis resulted. The utilization depends somewhat on the nutritional state of the patient, those witb malnutrition or starvation having poor ability to oxidize the sugar.

On injecting a liter of 10 per cent dextrose rapidly (in twenty-five minutes), Austin found a marked byperglycemia followed by a mild

hypoglycemia and an average loss of 13 per cent of the dextrose in the urine. When the same amount is injected in two hours the late hypoglycemia is more marked, though the average loss of dextrose in the urine is only 3 per cent. On injecting 200 cc. of 25 per cent solution in fourteen to thirty minutes, Heintzelman found hyperglycemia with an immediate increase in the blood volume, averaging 19.5 per cent, the volume and blood sugar returning to normal in about an hour. *Dextrose chills* are common from the intravenous use, the cause being not fully determined. They are mostly avoided by using the U.S.P. *water for injection*, which is distilled and sterilized within twenty-four hours of its use, and is free from pyrogens.

Pharmacologic Action.—*The Gastro-intestinal Tract.*—Shay et al. (1940) found that dextrose meals irritate the duodenum and delay gastric emptying. Manville and Munroe (1937), Carlson and others have reported inhibition of the hunger contractions even in the presence of high blood sugar. Manville and Munroe, by mouth doses, noted inhibition of the gastric secretion produced by sham feeding, or by histamine, pilocarpine or insulin, 5 Gm. being sufficient to check both secretion and motility. Noble and Robertson (1938) and Tudoranu et al. (1939) obtained a similar effect from high dosages of dextrose intravenously, but not from moderate amounts. Shay et al. (1934) found abnormal glucose tolerance curves from dextrose given to patients with gastric achlorhydria. Babkin reports that with intravenous dextrose the concentration of the enzymes of the pancreatic juice rises and falls with the blood sugar, an effect abolished by atropine and therefore presumably vagal.

The Liver.—This viscus requires carbohydrate, large amounts serving both to spare and to activate it (Mann). Consequently carbohydrate foods or dextrose are given in large amounts before operations on the liver. Wakim (1941) states that dextrose stimulates intrahepatic circulatory activity. Althausen (1938) reports that the higher the glycogen of the liver, the higher is its resistance to toxic agents, and that either oral or intravenous dextrose increases the deposition of glycogen both in normal rats and in rats with hepatic damage produced by phosphorus, unless the damage is extreme. With *intravenous dextrose* Baehr and Klemperer found more rapid repair of an injured liver after poisons such as arsenic. On the other hand, Jacobi et al. (1940) advised caution in the use of dextrose in the presence of liver disease, as intravenous dextrose depressed the flow of bile owing to an overload of the glycogenic function. Soskin and Hyman (1939) found that intravenous dextrose sufficient to raise the sugar in the afferent hepatic blood suppressed the liver function of producing blood dextrose from glycogen, so that one to three hours after stopping the dextrose, hypoglycemia may appear. They advise giving small amounts of carbohydrate during this

period. They found that insulin given to a non-diabetic produces no additional hepatic effect, but causes increased muscle glycogen storage. By this deposition the blood sugar is lowered and the liver consequently pours out more sugar, with a loss of glycogen. In toxic non-diabetic subjects they found that this shortened life.

The Heart.—In cardiac insufficiency, dextrose, especially with insulin, is administered as food to improve the glycogen reserve of the heart muscle. After 100 cc. of 50 per cent dextrose, Ellis and Faulkner (1939) found that the plasma volume increased 3 to 17 per cent, but began to fall in about one half hour. They consider intravenous dextrose a strain on the heart, and advise caution in its use in cardiac patients. On the other hand, Ginsberg et al. noted increased flow of blood through the coronary arteries, and in malignant diphtheria, with cardiac failure, Edmunds (1937) reports an immediate marked improvement in the heart and blood pressure. When the pressure falls it is restored by another injection. It should be given early, as Beck found that the cardiac changes come with low blood sugar. In diphtheria the glycogen and blood sugar are low (Lereboullet, 1922).

The Kidneys.—Strongly hypertonic solutions produce a hydremia by abstracting water from the tissues into the blood. If the dextrose is in sufficiently hypertonic concentration to produce glycosuria, the result is marked diuresis with increased chloride excretion.

Cerebrospinal Pressure.—Tilney, Kennedy and others find that, by causing diuresis, highly hypertonic solutions deplete the cerebrospinal fluid. But in many cases Jackson et al. obtained an increase in the pressure, and Masserman, with 100 to 200 Gm. in 20 to 35 per cent solution in a large number of patients, noted an initial rise in pressure, then a fall, and later a rise which at three hours was 8 to 148 mm. of water above normal. Unlike sucrose, dextrose penetrates into the cerebrospinal fluid, and is nearly all hydrolyzed in the body. As a consequence, its value is soon lost, and there is a resulting secondary rise in intracranial pressure. From 50 per cent *sucrose* Masserman obtained a prolonged fall in pressure.

The Ovaries.—Tedstrom and Wilson report premenstrual irritability and dysmenorrhea when the fasting sugar is below 80, and its relief by sugar or intravenous dextrose.

Barbour and Howard obtained an *antipyretic* effect, the result of a plethora which promoted heat elimination. MacLeod observed a lactic *acidosis*, and Schultz and Bliss found that dextrose given one half to one hour before exercise depressed the fixed acid that otherwise rises from exercise. Lactose and sucrose failed to have this protective effect.

Allergy.—*In allergics,* Malone (1929), and Black (1933) reported low blood sugar, 61 to 80, and Stoesser and Cook found it valuable in *bronchial asthma,* but not in that due to pollen. Stout and Koschitek

(1940) obtained immediate relief in *serum sickness, urticaria,* and all kinds of itching.

Therapeutics.—*By mouth,* it is of especial value in *malnutrition, cardiac insufficiency, hepatic disease, hepatic intoxications* as from the arsphenamines, and before and after *operations about the liver.* To supplement a high carbohydrate diet, 100 Gm. a day may be given in fruit juice.

Intravenously, in 5 to 10 per cent solution, it may be used for the same purposes, particularly when conditions preclude its administration by mouth, as in *uncontrollable vomiting, inanition psychosis, insulin hypoglycemia, severe fevers, severe toxemias* (especially eclampsia, the pernicious vomiting of pregnancy, uremia, and acute liver conditions), in *acidosis* from starvation or following general anesthesia, and *post-operatively.* At the rate of 300 to 500 cc. an hour, 95 per cent is utilized (Winslow, 1938).

Intravenously, in 20 to 50 per cent solution, it is employed in (1) *diabetic coma,* (2) *the acute toxemias,* (3) as a diuretic in *anuria* and *cardiac and nephritic edema,* and (4) *to reduce intracranial pressure,* as in skull fractures, meningitis, brain tumor, acute cerebral edema and encephalitis.

Preparations.—U.S.P.—*Dextrose; injection of dextrose; injection of dextrose and sodium chloride.* The strengths of the injections are to be prescribed by the physician, and they must meet the U.S.P. requirements as to sterility and the absence of pyrogens.

SUCROSE

Sucrose, U.S.P. (cane or beet sugar) is soluble in one half part of water and 170 of alcohol. It is used as a nutrient and sweetening agent, and in the manufacture of syrups, elixirs, hypodermic tablets, etc. *Syrupus, U.S.P.,* is a saturated aqueous solution.

In the stomach, sucrose increases the viscosity of the gastric contents, lowers secretion and motility, prolongs the emptying time, and by retarding digestion favors the development of a hyperirritable condition. It is readily absorbed in the duodenum after undergoing inversion, but may decompose in the intestines with the production of fatty acids and carbon dioxide gas. In guinea pigs Cattell found that the fatty acids might be laxative, while a solution of sugar placed in the intestines unfermented, retarded peristalsis. Through this acid production sugar favors the absorption of calcium, phosphorus and iron.

Given *intravenously* sucrose does not hydrolyze and is excreted unchanged in the urine, 78 to 92 per cent appearing in twenty-four hours. On this account intravenous sucrose is not nutritive, has no glycogenic action, and has no power to prevent the rise of lactic acid in the blood which follows exercise. Helmholz found large amounts

toxic to rabbits, with the production of hydropic degeneration of the convoluted tubules of the kidneys and a narrowing of their lumens. Lindherg et al. (1939) found the same in dogs. Helmholz reported death in a boy, and Anderson and Bethea found six cases at autopsy, showing the same lesions. Sucrose is strongly *diuretic*, the urine obtained approximating 130 per cent of the volume of the liquid injected. Helmholz and Bollman (1939) found solutions of sorbitol, dextrose, urea and sodium sulfate, of equivalent tonicity to 20 per cent sucrose, less diuretic, and all except sorbitol definitely more toxic.

Therapeutics.—Intravenous sucrose has come into use as an osmotic dehydrating agent, *to reduce intracranial pressure*, especially in brain injuries, uremia, eclampsia, etc.; to overcome the cerebral effects of serious arterial hypertension, such as headache, vertigo and vomiting, and to reduce intraocular tension in glaucoma. Shelburne et al. found an almost constant association between excessively high diastolic pressures and high intraspinal pressures. It does not penetrate to the cerebrospinal fluid, at least more than a trace, and as it is not burned in the body its effect may be prolonged for twelve hours or more. The drop in pressure is not followed by a secondary rise, as it is with dextrose. In brain trauma cases, Jackson et al. obtained a 50 per cent reduction in the pressure. Tbe plasma volume rises and may not fall till diuresis sets in, a possible danger in cardiac cases. In uremia with anuria it may be valuable. In a dog with kidneys affected by bichloride of mercury poisoning, Strohm (1937) observed a douhling of the urinary output.

According to Jackson et al. the intravenous dose is 200 to 300 cc. of 50 per cent, or larger amounts of 20 per cent. Hahn et al. consider 100 cc. of 50 per cent sufficient.

SORBITOL

The related substance, *d*-sorhitol, $C_6H_{14}O_6$, is not a true carhohydrate, hut rather a sugar-alcohol. It is the hasal suhstance from which ascorhic acid is made. It has been employed as an osmotic dehydrating agent in the same conditions as sucrose. Theoretically, on account of its molecular weight, which is 342 as compared with 182 for sucrose, it should have nearly twice the dehydrating power of sucrose, hut is somewhat hydrolyzed in the hody so that not more than 50 per cent is recovered from the urine. This of course is hetter than with dextrose which is nearly all hydrolyzed. It does not penetrate into the cerehrospinal fluid or the intraocular spaces. While several experimenters have reported good results these have bcen variahle, Helmholz and Bollman, for example, finding it less diuretic, though not more toxic than sucrose. Its value at present is *sub judice*. The intravenous dosage is 100 cc. of 50 per cent.

AMINO ACIDS

Amino acids, $(R-\underset{NH_2}{\overset{H}{\underset{|}{\overset{|}{C}}}}-COOH)$, are the end products of the digestion of proteins in the alimentary tract. Absorbed from the intestines they pass directly to the liver and there and elsewhere are synthesized for the most part into proteins, which pass to the blood. *They are not drugs but foods*, and they furnish most of the nitrogen, not only for protein, but for all the nitrogenous materials of the body. Normally there are large reserve stores of amino acids or proteins in liver, muscle and other tissues. But these reserves may be depleted by (1) *Inadequate protein intake* in the food. (2) *Faulty digestion.* (3) *Malabsorption.* (4) *Increased protein need*, as in rapid growth, pregnancy, lactation, and hyperthyroidism. (5) *Increased protein loss*, as in albuminuria, edema, ascites, serum exudation, hemorrhage, shock, burns, bed sores, fever, kidney disease, trauma and surgery. (6) *Impaired protein synthesis*, as in infections and liver disease. Elman et al. (1940) state that for every gram of loss in plasma protein there is a tissue protein loss of 30 Gm.

Ten amino acids not synthesized in the body, but considered "essential," a classification based originally on growth in rats (Rose), are: Arginine (synthesized but not in adequate amounts), histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane and valine. In humans Rose et al. (1943) found arginine and histidine unnecessary for the maintenance of N equilibrium. All are crystalline and levorotary. A mixture of these amino acids, combined as in the protein imitated, never has a biological value equal to that of the protein itself (Rose, 1938, Murlin, 1945). Their deficiency, however, results in *hypoproteinemia*, which, on account of the lowered osmotic pressure of the blood, is a main cause of edema.

According to Co Tui and Wright (1944) intravenous amino acids in dogs diffuse from the blood into the extracellular tissue very rapidly, but the amino acid level in the blood rises sooner and to a greater degree after amino feeding than after food feeding. Madden et al. (1946) report that amino acids are not so well utilized parenterally as orally, and are less well utilized than natural foods.

Therapeutics.—The indication for amino acids is *severe hypoproteinemia*, but only in conditions in which the feeding of proteins is impossible, inadequate or undesirable. There is no evidence that the amino acid digestates (hydrolysates) are superior to food (Peters, 1945).

In normal infants on a protein free diet Shohl et al. (1939) established a positive nitrogen balance with hydrolized casein. In the

nutritional edema accompanying hypoproteinemia Elman and Wiener (1939), finding a failure of absorption from the oral administration of proteins because of edema of the intestines, had great success with intravenous injections of a hydrolysate of casein, fortified with 2 per cent of tryptophane and 2 per cent of either methionine or cystine. In non-healing ulcers, burns and muscular dystrophies, and postoperatively, Altschuler et al. (1943) had good results from a similar fortified preparation. They found that given before operation the amino acids protect the liver from the toxic effects of an anesthetic. Several investigators have found them prophylactic against liver poisoning by chloroform, carbon tetrachloride, arsenicals and sulfa drugs. Koster (1943) reports twenty-five operative patients kept in nitrogen equilibrium by intravenous amino acids with dextrose. In 352 patients with serious abdominal operations, Elman et al. (1945) report 2739 intravenous injections of hydrolysate and dextrose furnishing 12 Gm. of nitrogen a day. In some patients nitrogen equilibrium was maintained, in others there was a loss of 1 to 6.8 Gm. a day, while from dextrose alone the loss was 10 to 25 Gm. In dogs with hypoproteinemia and anemia Whipple et al. (1943) found the essential amino acids satisfactory, not only for the regeneration of plasma proteins, but also for that of hemoglobin.

Peptic Ulcer.—Hoelzel and DaCosta (1932) discovered a relation between the development of ulcer and protein deficiency in rats. Matzner et al. (1938) found that protein foods were protective against experimental ulcer. Levy (1945) used oral amino acids for bleeding ulcers. Co Tui (1945) proposed the use of oral amino acids for the treatment of all severe ulcers. But that in ulcer treatment the hydrolysates are better than milk and egg feedings has not been clearly demonstrated.

Toxicology.—In experimental work toxic actions have not been noted, but there are on record at least two fatalities following an intravenous dose of a hydrolysate, both apparently in patients with severe hepatic damage (Hoppe and Campbell, 1943, Curreri et al., 1945).

Administration and Preparations.—As the mixtures of pure amino acids are too expensive, *digestates (hydrolysates)* of various proteins, with dextrose, and added tryptophane and methionine (or cystine), have been utilized. The lack of a single needed amino acid may be disastrous (Rose). The pancreas digestates of casein, lactalbumin, defatted dried beef muscle, and wheat gluten are being studied. It is considered that digestates from more than one food are superior to those from one food only.

Oral preparations are relatively weak, decidedly unpalatable, and "prone to produce nausea, distention, cramps and diarrhea" (Co Tui, 1946). They are usually taken mixed with flavored water or

vegetable juices, fruit juices being unsatisfactory. A heaping tablespoonful may give 3 or 4 Gm. of nitrogen. Elman (1943) used them with benefit in patients in whom whole protein by mouth is inadequately digested, in those who can be fed only through a tube passed into the jejunum, and in those whose nutritional deficiency is such that rapid treatment is necessary. Co Tui employed them in peptic ulcer patients.

Intravenous preparations are for emergency. As the amino acids go through the organs before reaching the liver, there is a loss in the urine, but this is largely avoided by slow injection. Martin and Thompson (1943) gave 10 Gm. per hour and Elman et al. 25 Gm. without essential loss in the urine. The daily dosage is 35 to 150 Gm. In dogs, Silber et al. (1946) found a loss of 13 per cent in the urine when the acids were administered at the rate of 12 mg. of N per Kg. per minute, but a loss of only 4 per cent when given at the rate of 2 mg. per minute. In edema and malnutrition cases there must be limitation of salt and the total amount of fluid, even in the presence of dehydration (Evans and Shulman, 1940). Coller and Maddock's rule is: For each 100 mg. that the plasma chloride level needs to be raised to reach normal (500 mg. per 100 cc.) give 0.5 Gm. of sodium chloride per Kg.

Amino acids are sometimes administered subcutaneously, intramuscularly, intrasternally, or by duodenal tube. Rectally their absorption is too uncertain.

The U.S.P. Amino Acid Advisory Board (October, 1946) gives a tentative description for a superior preparation which may be epitomized as follows: *Protein Digestate Parenteral* is a sterile, non-pyrogenic solution of a non-antigenic preparation of hydrolized protein. It is a clear solution of pH 6.0 to 6.7, and must contain not less than 12 per cent of nitrogen, of which not less than 50 per cent is in the form of alpha amino nitrogen. It must respond to tests for rat growth, and for its ability to make up nitrogen deficiency in dogs given a non-protein diet. Injected into dogs in a specified manner it causes no significant changes in blood pressure or respiration, and causes no vomiting or other sign of abdominal distress. It may contain added dextrose, mineral salts, or specific amino acids.

Methionine and Cystine

The need of the body for sulfur is not met by inorganic sulfur, but by organic sulfur in the food, largely supplied by the amino acids, methionine and cystine. Methionine has 21.5 per cent of sulfur and cystine 26.7 per cent. Cysteine is a reduced form of cystine. Cystine may be synthesized in the body, methionine not; and cystine is essentially a product of methionine. Cystine is high in the posterior

pituitary hormones and in skin, nails and hair, and constitutes about 12 per cent of insulin.

Of these sulfur containing bodies methionine is the most important. The absence of methionine leads to complete nutritive failure and death, an effect not prevented by cystine, since in the absence of methionine from the diet cystine is not capable of growth promotion. So while a cystine need may be completely satisfied by methionine, the latter cannot be replaced by cystine. Indeed, methionine is looked upon as the key amino acid in protecting the liver in its functions of deamination and plasma protein synthesis.

In addition to sulfur, methionine furnishes methyl groups, and may be converted into the lipotropic choline, a compound with three methyl groups attached to the nitrogen of its molecule. By their methyl groups, both methionine and choline can contribute to the formation of creatine and to muscle metabolism. Either can protect against fatty degeneration of the liver and cirrhosis, and against hemorrhagic kidney degeneration, and either can be converted into the other. (See also Choline.)

Therapeutics.—In chloroform anesthesia in protein deficient dogs Miller and Whipple (1942) prevented liver damage by intravenous administration of 3 Gm. of methionine. Beattie et al. (1944) used it with success in carbon tetrachloride poisoning. It prevents excessive tissue breakdown after severe burns, and is of value in post-arsphenamine jaundice and toxic liver disease. It helps damaged liver to inactivate estrone (György, 1946). It has proved useless in infectious hepatitis and ileitis.

Methionine is used as a 2 per cent addition to protein digestates (hydrolysates), may be added to the diet, or may be given in capsules or in aqueous solution, by mouth or intravenously, in doses of 2 to 3 Gm. a day. Cystine has been used for the same purposes in the same dosage, but is inferior. (For methionine in liver disease see Choline.)

CHOLINE

Choline, $(CH_3)_3N.CH_2.CH_2O$, is not an amino acid, but its close relation to methionine permits its introduction here. It is also classed with the B-vitamins. Lecithin contains choline, and casein contains both choline and methionine.

Best et al. noted that administration of choline would lower the excess of liver fat in depancreatized dogs, and prevent the fatty liver changes following carbon tetrachloride poisoning. In choline deficiency in rats, Griffith et al. observed fatty liver, degeneration in the renal tubules and glomeruli, renal cortical hemorrhage, enlarged spleen and arrested growth. In the order of development the effects of a choline deficient diet (Bennet, 1945) are: fatty liver, cessation of growth, hemorrhagic or nephrotic kidneys, and depressed vagal

function. Choline acts in the liver by its incorporation as an intact unit in the molecule of the phospholipid lecithin, in which form the fats of the food are passed to the blood. Best states that in choline deficiency there is not necessarily decreased oxidation of fats, but rather delayed fat transport. Methionine has about one-fifth the lipotropic activity of choline (Channon et al., 1940). Choline is important in the methylation of homocystine to methionine, and is related to sulfur and fat metabolism.

The Blood.—Davis (1944) reported that choline chloride given to dogs, 10 mg. per Kg. per day for twenty-five days, resulted in a hypochromic anemia. But Cartwright and Wintrobe (1945) gave it for ninety days to three men who did not have liver disease, and observed no hematologic changes. In a patient with cirrhosis of the liver and macrocytic anemia Watson and Castle (1945) gave 17 mg. per Kg. daily (1 Gm. a day) for seventy days, with continued improvement of the hemoglobin and red cell count.

Therapeutics.—*Fatty Liver, Cirrhosis of the Liver.*—It is agreed that, on account of the loss of the proteogenic function of the liver in these conditions, dietary protein does not suffice for the body's needs. The hypoproteinemia is due to this loss of fuoction rather than to loss of albumin in ascitic fluid; for in a patient Barrett et al. (1932) removed ascitic fluid representing 10.2 Gm. of protein a day for 204 days, without materially lessening the proteins of the blood.

Lowry et al. (1941), in experimental cirrhosis in rats, found that the addition of choline to the diet resulted in hyperplastic regeneration of the liver cells, with disappearance of degenerative fatty changes. Beams (1946) gave twenty patients choline, together with cystine or methionine, and in two or three months, in those with enlarged liver, presumably fatty, the ascites was gone and the liver was much smaller. The serum albumin had been 2.47 to 3.08 Gm. per 100 cc. and it rose to 3.4 to 4 Gm. But the treatment was of no value when massive fibrotic changes had taken place in the liver. Morrison (1946) gave 2 Gm. of choline and 2 Gm. of methionine daily to twenty cirrhosis patients, together with liver extract and vitamins, and a high protein, high carbohydrate and low fat diet. In three months in those patients without ascites, there was a remission in all signs and symptoms in 64 per cent, and in those patients with ascites in 34 per cent. It would seem that choline is valuable treatment for fatty liver, and for fatty liver with cirrhosis.

Preparations and Administration.—*Choline* is a viscid strongly alkaline liquid. *Choline chloride*, the substance employed, is crystalline and freely soluble in water and alcohol. It is neutral to litmus. The chloride is given in capsules or in solution in a total dosage of 1 to 2 Gm. (15 to 30 gr.) or more daily. Russakoff and Blumberg gave a patient 6 Gm. a day for six months without adverse effects.

Lecithin

Lecithin, not an amino acid, is a phospholipid, which contains in its molecule linoleic and other fatty acids, cephalin, inositol, cholesterol and choline. It furnishes choline and promotes the absorption of fats. There are minor differences in favor of soybean lecithin over that from egg. Giving defatted lecithin, Gross and Kesten (1943) and Adlersberg and Sobotka (1943) obtained a reduction of the blood cholesterol in man when there was hypercholesteremia, but not a reduction of normal cholesterol. Hoagland (1943) used it successfully as a choline furnisher in the treatment of cirrhosis of the liver. Gross and Kesten and others have reported good results in psoriasis, and in certain other skin conditions, such as keratoses, scleroderma, senile atrophy and the seborrheas. Dose, 15 Gm. a day by mouth.

Aminoacetic Acid

Aminoacetic Acid, N.F., (*glycine, glycocoll,* CH_2NH_2COOH), an amino acid, contains about 18.5 per cent of nitrogen and is soluble in 4 of water, dose 30 Gm. (1 ounce). The *elixir, N.F.*, contains about 13 per cent. Glycine constitutes 25.5 per cent of gelatin and 3.5 per cent of serum globulin, and converts benzoic acid to hippuric acid in the liver, a function used for testing liver efficiency. Glycine and cystine are the amino acid precursors of bile salts. At one time glycine was strongly advocated as a creatine and muscle builder. In two patients on 4 Gm. a day for two weeks, Wilder (1934) found the creatine excretion reduced one-third and four-fifths, and personally found it helpful in his own athletic activities. Acre (1940) obtained increased physical endurance and brighter mental states. But most investigators have had negative results. From dosages up to 45 Gm. a day, Viets and Schwab (1939) declared it without value in seventeen patients with myasthenia gravis. Horvath et al. (1941) found no change in the grip strength of eight men given 6 to 12 Gm. a day for several weeks. King et al. (1942) determined it valueless in doses of 6 Gm. a day given to 33 football players and tested by the bicycle ergometer. They found that it could produce creatine only with the addition of methionine.

Gelatin

Gelatin, U.S.P., a protein obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals, comes in sheets, flakes or powder. The isoelectric point of that derived from an acid-treated precursor is between *p*H 7 and 9, and of that from an alkali treated precursor *p*H 4.7 to 5. It is soluble in boiling water and in the proportion of one part to 50 of water forms a jelly on cooling. In cold water it absorbs water and swells, but does not dissolve. It is precipitated by tannic acid as a tough,

leathery mass. It is used for capsules and pill coatings, and as a food substance.

Gelatin is an incomplete protein, but contains 25.5 per cent of aminoacetic acid (glycine), and may possibly furnish material to make new plasma proteins. It is deficient in tryptophane and methionine, and in other essential amino acids. Hier et al. (1944) obtained less growth with gelatin added to essential amino acids than from the amino acids alone. King et al. find that the claims for a special value of gelatin in increasing endurance or the treatment of fatigue are unfounded.

Therapeutics.—A 1 per cent addition of gelatin to cow's milk for children results in smaller and softer curds in the stomach. It tends to increase the viscosity and coagulability of the blood, and has been administered by mouth in *bleeding peptic ulcer*, and intravenously in *internal hemorrhage* and *aneurysm*. However, as it may contain resistant bacterial spores and cannot be long exposed to heating, sterilization is uncertain, so it is not recommended for intravenous use. For *Gelatin Sponge* as a hemostatic see "Coagulants." *Glycerinated gelatin, U.S.P.*, equal parts of glycerin and gelatin, is a soft rubbery mass which melts at body temperature, and is used as a basis for vaginal suppositories.

HISTIDINE

Histidine is an amino acid constituent of most of the simple proteins, and occurs in beef, fish, eggs and milk. Large amounts appear in the urine in pregnancy, and in hepatic and allergic disorders. On the unsubstantiated theory that peptic ulcer is due to a deficiency in amino acids, and without scientific evidence that there is such a deficiency in ulcer patients, *histidine monohydrochloride* (*larostidin*), a proprietary remedy, has been introduced for the treatment of this condition. It is furnished in 4 per cent solution for intramuscular injection and in tablets for oral dosage. The injection method is the one regularly employed, a dose of 4 or 5 cc. being given daily for about twenty-four days. It is claimed that the patient does not require restrictions in the diet.

Comparisons with treatment by the older diet-alkali regimens have failed to substantiate the alleged advantages of histidine. After ulcer-producing procedures, Mann et al. and Sandweiss et al. in dogs, and Windwer and Matzner in rats, found no ulcer-preventive effect. From a study of eighty-one patients, Martin (1936) reported that the symptomatic and radiologic response of forty-one patients on the histidine treatment was not quite so good as that of forty controls on the diet-alkali regimen, in either the initial or the sustained effects. Ten months later, of the thirty rendered symptom-free by histidine only thirteen had remained so, and in the forty-one cases

treated there bad been twenty-six recurrences. With sixty-seven patients, some under histidine and some on the diet-alkali regimen, Sandweiss had similar results.

Histamine

Histamine, beta-iminazolylethylamine, a normal constituent of the body, is a derivative of tbe amino-acid histidine, by decarboxylation, a change which may occur in the body. It is soluble in water and alcohol, and is thermostable. It is found in most of the tissues, especially liver, lungs, hypophysis, and the walls of stomach and intestines. It is also formed in the digestive tract by the action of bacteria on histidine, and is abundant in moldy and decomposed ergot.

Anaphylaxis.—Histamine shock of the anaphylactoid type, with severe asthma, is so readily produced by intravenous doses, that Lewis and Dale have thought histamine the ultimate poison of all specific sensitiveness, the antibody-antigen liberating it from its loose combination in tbe tissues. Hanzlik and Karstner attributed the anaphylactoid symptoms to blood platelet thrombi.

Action.—It tends to stimulate smooth muscle, notably that of the bronchi and uterus, to increase the gastro-intestinal secretions, and to dilate arterioles, venules and capillaries, producing, in the skin, flushing or urticaria, and systemically, collapse. Some investigators believe that it is formed in damaged tissues, and is an important producer of traumatic shock.

When injected into or beneath the skin it has a *local* vasodilator action, causing redness followed by a wheal which throws out pseudopods along the lymphatic channels. It is rapidly absorbed into the blood stream, from which it disappears quickly into the tissues. *Systemically,* vasodilation, chiefly of capillaries, is marked in the structures of great vascularity, the skin, mucous membranes, liver, spleen, lungs and brain.

In man, following an intravenous dose, and sometimes from as little as 1 mg. subcutaneously, there may be immediate flushing of the skin, palpitation, dull throbbing headache, nausea, sweating, dizziness and prostration. It increases the flow of saliva, gastric juice, pancreatic juice and succus entericus. It stimulates gastro-intestinal motility and is prone to induce bronchial constriction with asthmatic dyspnea. Urticaria may appear at the site of injection or elsewhere. In the blood cholesterol falls and epinephrine and blood sugar are increased.

Best and McHenry (1930) discovered histaminase, which they thought was an enzyme for destroying histamine in the body (see discussion under Histaminase). But according to Martin et al., (1943) the physiological detoxicants of histamine are cystine, glycine, ascorbic acid and calcium glycuronate. Tolerance may be con-

siderably increased by repeated doses, and in some cases a state of refractoriness to histamine develops.

In the stomach it stimulates the motility and the production of gastric juice, and as it directly affects the parietal cells, this secretion is of high acidity. The amount of pepsin is slight and is thought by some to be merely the preformed pepsin washed out by the secretion. Alley believes that histamine inhibits the peptic cells. The amount of mucus is low. In cases of achlorhydria it is a common clinical test to inject subcutaneously 0.5 mg. of a histamine salt, and if no gastric acid is produced within an hour to consider that complete achylia gastrica is present. The test is not infallible as in some cases refractoriness to histamine is manifest (Palmer et al., 1940). Overgaard (1933) found that dogs given daily injections while fasting developed an antral gastritis, but not if food was given with the drug. By creating a continuous acid effect in dogs with histamine in beeswax, Walpole et al. (1940) produced erosions and ulcers in the upper digestive tract. To stimulate gastric secretion by *oral* doses in man, Lim, Ivy and McCarthy found 100 to 225 mg. necessary. *In the liver* there is much histamine, and this organ furnishes it to the blood in anaphylactic shock (Dragstedt et al.). On the *uterus*, from a solution of 1:600,000, Lieb obtained powerful contraction with temporary tetany.

Toxicology.—Generalized urticaria, severe dyspnea from bronchial spasm, severe vasomotor reactions or collapse have been noted. The antidote is epinephrine, of which 1 mg. in the blood will neutralize the effect of 10 mg. of histamine. For the bronchial spasm ephedrine and aminophylline have proved effective. Maijala (1938) reports death from the subcutaneous injection of 0.8 mg. in testing a patient's stomach. A number of profound reactions have followed the use of 1 mg. in this test, so that the testing dose is now regularly kept at 0.5 mg.

Therapeutics.—On the theory that various conditions are precipitated by the release of histamine into the blood as the result of anaphylaxis or allergy, histamine has been employed in small increasing dosage as a desensitizer in recurrent allergies. But according to Thomas and Butler (1916) as it is not a protein it cannot produce sensitization or allergy or bring about desensitization. Nevertheless, when administered in sufficient dosage it itself gives reactions typical of allergy.

It has been recommended specifically in: (1) Neurovascular headache. (2) Ménière's syndrome. (3) Vasomotor rhinitis. (4) Multiple sclerosis (Mayo Clinic). (5) Chronic urticaria, eczema, angioneurotic edema, asthma, hay fever, serum sickness and allergic reactions traceable to heat, cold, food, etc. In ointment form and by iontophoresis it has been employed locally for the pain of arthritis on the

theory that it provokes local vasodilation. In spite of many laudatory reports, the drug has not come into extensive favor with clinicians.

Preparations and Doses.—U.S.P.—*Histamine phosphate*, (36 per cent histamine), soluble in water and alcohol. *Injection of histamine phosphate*, 1 cc. equals 1 mg., designed for testing the acid secreting power of the stomach. Diluted with isotonic salt solution histamine and its salts have been employed, intravenously or by hypodermic, in increasing dosage, to overcome histamine allergy. Beginning with 0.05 mg. intravenously twice a day, the dose is raised by 0.01 mg. each day till 0.1 mg. is reached. It is then continued twice a day for two or three weeks. A proprietary ointment for arthritis is also available.

Anti-Histamine Drugs

These are of two classes: (I) Those that specifically desensitize against histamine; (II) Those that block the action of histamine and give symptomatic relief in allergic attacks.

In Class I, those that desensitize, are (a) minute doses of histamine (See Histamine), and (b) hapamine, a proprietary histamine azoprotein compound, which contains no free histamine and does not give any typical histamine reactions. These drugs induce the production of histamine-specific antibodies. Of hapamine, beginning with such small doses as 0.01 to 0.02 cc. every four days, the dose may be increased by 0.01 cc. every four days till it reaches 0.1 cc. Then it is increased by 0.1 or 0.2 cc. till the dose is 1 to 1.5 cc. every four days.

In Class II, those that block the action of histamine before the attack or at the time of the attack, but do not desensitize, are histaminase, benadryl, pyribenzamine and related bodies.

Histaminase

In 1930 Best and McHenry reported that almost every tissue contains a histamine inactivating substance which they called histaminase. Its richest sources were the kidneys and the intestines. Immediately it was hailed as a treatment for alleged histamine intoxication. Ten years later (1940) Best and McHenry wrote substantially as follows: The administration of histamine to animals for some weeks has no effect on the histaminase content of the kidneys. It gives no protection to guinea pigs against anaphylactic and histamine shock. Histaminase is inactivated by pepsin in acid solution and by trypsin in slightly alkaline solution, therefore its oral administration (even in enteric coated tablets) is of no value. Our investigations over a period of ten years have failed to show that intra-

venous or intramuscular administration of histaminase has any effect on the histamine present in the body or on that given by injection. There is no physiological basis on which to rest its use, and no indication that it is useful therapy.

As with all new remedies there are a number of favorable reports. For example, Roth and Horton (1940) say "Histaminase seems to be an effective therapeutic agent in certain cases of clinical hypersensitiveness," referring especially to cold and heat allergy, serum sickness, urticaria, vasomotor rhinitis and cephalalgia. Atkinson, Ivy and Bass (1941) used it intramuscularly in dogs and orally in humans. In eight humans 50 units in enteric coated capsules three times a day for three days had no effect on gastric secretion. Knies and Pritchett, (1941), using the gastroscope, concluded that histaminase does not modify the gastric secretory response to parenteral histamine. Necheles (1940) found that any effect of histaminase was not due to the destruction of histamine. Katz (1942) thinks that the reason for its ineffectiveness is that it takes hours to act, while histamine acts in seconds or minutes.

No preparation of histaminase is official. *Torantil,* a proprietary extract from the mucosa of the small intestines and desiccated kidneys of hogs, is claimed to contain histaminase in active and stable form. The tablets are enteric coated. The dose is 10 to 15 units three times a day, a unit being the amount that will inactivate 1 mg. of histamine hydrochloride during incubation at 37.5° C. for twenty-four hours.

BENADRYL

Benadryl, beta-dimethylaminoethyl-benzhydryl ether hydrochloride, not official, is an anti-histamine substance of a new order. It has been tested extensively at the Mayo Clinic (1945) and by others, both on animals and on human beings. Its noteworthy actions are: (1) To alleviate the bronchial constriction and asthma of histaminic or anaphylactic shock. In this action it is found to be 15 or 30 times as effective as aminophylline. (2) To relieve the vasodepressor effects of histamine. (3) To relax smooth muscle. It tends to overcome the dilatation of the capillaries and their increased permeability, the histamine stimulation of the lachrimal, nasal, pulmonary and digestive secretions, and the local edema which shows in urticaria, angioneurotic edema, hay fever, vasomotor rhinitis, sinus disease, and Ménière's symptom complex.

In normal humans on 100 mg. by mouth four times a day there has been no effect on the heart beat, pulse rate, circulation time or the electrocardiogram, and no change in the level of hemoglobin and the red and white cell counts. Oral doses have little if any effect on the gastric secretion of hydrochloric acid induced by histamine. In the intestines it antagonizes acetylcholine and barium chloride.

Untoward Actions.—There is a sedative action on the cerebrum which results in marked drowsiness in many who are taking full dosage, and may require treatment with caffeine, amphetamine or ephedrine. Also noted are nausea, especially if taken on an empty stomach, dry mouth, dizziness, nervousness and numbness of the extremities. Cases are reported of muscular twitchings and spasticity of the extremities, disorientation, hysterical reactions and serious collapse. In animals lethal doses, which are large, produce violent excitement, convulsions, respiratory failure and death.

Therapeutics.—Theoretically it is active only when there is an excess of histamine in the blood, but it has given good results in some cases where an excess of histamine could not be established. Its uses are: Urticaria, angioneurotic edema, asthma, hay fever, vasomotor rhinitis, sinus attacks, reactions to serum, contact dermatitis, erythema multiforme, dysmenorrhea, migrainal headache, myalgia of the head, irradiation sickness, Ménière's symptom complex, hypersensitiveness to cold and heat, and various forms of pruritus.

Administration and Dosage.—Ordinarily it is given by mouth, in doses of 25 to 100 mg. three or four times a day. In night pruritus 100 mg. may be given at bedtime. Intramuscularly, it may be given in a solution of 10 mg. in 1 cc., but it is locally irritating. Intravenously it has been given by continuous drip or by injection of physiological solution of sodium chloride containing 50 or 60 mg. in 100 cc.

PYRIBENZAMINE

Pyribenzamine, N, N-dimethyl-N'-benzyl-N' ethylenediamine, is another chemical with strong anti-histaminic properties. Its actions and untoward actions are similar to those of benadryl, and its therapeutics and dosage the same. It has received less study than benadryl, but apparently produces less nausea and drowsiness.

VITAMINS

The vitamins constitute a group of unrelated chemical substances that in minute amounts exert a profound influence upon and are necessary for various body functions and the structural development of animals. They are requisite for nutrition, growth and reproduction. A marked vitamin deficiency produces definite symptoms; a slight deficiency may not be recognizable clinically.

So much research work is being done upon vitamins, so many new facts being brought forward almost daily, that it would require a volume to tell what is known up to date. The early familiar ones have been separated into a considerable number of individual substances, and new ones have been discovered. Of many the chemical nature has been determined and chemical names given them, so that the old names A,B,C,D,E, etc. will soon be abandoned. Many have

been made synthetically. Of the original vitamin B at least twelve components are known, and of vitamin D there are ten forms, of vitamin E, three, and of vitamin K, four. Vitamin F, a mixture of linoleic and other fatty acids, is no longer considered a vitamin; vitamin G is riboflavin, and H has been applied to several different substances, especially biotin. The ones that we must have for growth, health and reproduction are A, B, C, D, E and K. The Food Nutrition Board of the National Research Council expresses the *minimal daily needs* of vitamin for an active man of 70 Kg. (154 lbs.) eating 3000 calories a day, as follows: Vitamin A, 500 units; thiamine, 1.8 mg.; riboflavin, 2.7 mg.; niacin, 18 mg.; ascorbic acid, 75 mg., and vitamin D, 400 to 800 units.

Vitamins are not medicines in the ordinary sense, like digitalis and caffeine, but are normal ingredients of our foods. They are to be obtained from food when possible, and prescribed by themselves only when the food is deficient. But the students of nutrition are finding numerous instances of mild vitamin deficiency in our population. Therefore, since vitamins in ordinary amounts are not known to do harm, drug store vitamins may properly be prescribed for those not in robust health, and especially for those who consume habitually insufficient foods or one-sided diets, or are ordered such because of illness. They are especially beneficial for the very young and the elderly. The Army is using them in large quantities. Moreover, they are not expensive, for one or two tablets a day of mixed vitamins cost only a few cents, less than similar doses of ordinary medicines. One advantage over food vitamins that prescription vitamins possess is their standardization by the U. S. Pharmacopoeia, and the enforcement of these standards by the Food and Drug Administration. In any event, however, no amount of store vitamins can take the place of an adequate diet.

The vitamin content of foods depends greatly on factors in their production. The vitamins in eggs, milk, and meat vary with the diet of hen, cow or other animals; those in vegetables and fruits, with the soil and weather conditions, and all depend on the season. In winter, in northern climates, added vitamins may be especially needed, for those of milk and eggs are relatively low and sunlight is inadequate. In northern New York and in Ontario, the sun's rays were found so low from October to April that they would not tan the skin. It was estimated that twenty minutes of the sun at noon in June equalled three or four hours of the sun in January. In milk, Dornbush et al. (1940) found only about half as much vitamin A and carotene from January to April as from June to October. In June Campion et al. (1937) found 17 to 26 units of vitamin D per quart of milk from cows kept outdoors and 5 to 8 units from cows kept indoors. In February, in the yolk of egg, deVaney et al. (1933) found 140 units of D, and in June 390 units.

Cancer and Vitamins.—Kinosita et al. (1940) demonstrated that butter yellow (N, N-dimethylaminoazobenzene) regularly caused liver cancer in rats fed on polished rice with carrots, but not if liver and yeast were added to the diet. Thus was established a relation between cancer susceptibility and the diet. György reported that when the diet contained rice, either polished or unpolished, the animals developed cirrhosis of the liver instead of cancer. Rhoads et al. found that butter yellow caused a prompt and serious decrease in coenzyme I (diphosphopyridine and nucleotide) of the liver, which is concerned with fermentation and depends on nicotinic acid as an essential component.

Biotin, a B complex vitamin, occurs in large amounts in liver and milk, and to some extent in egg yolk. In the body, it is found in greatest concentration in the fastest growing tissues, which are prolific producers of cancer (West and Woglom, 1941), and in high concentration in cancers developed in these tissues. In white rats maintained on diets affording a high degree of protection, especially the B vitamins, and given butter yellow, Rhoads and duVigneaud (1942) noted the development of liver cancer in one of twenty-eight rats. When biotin was given, twenty-two of fifty rats developed cancer. Patients with cancer, especially sarcoma, who have developed erysipelas, have experienced regression of the tumor in some instances. It is now found that the bacteria which cause erysipelas use up a lot of biotin.

Avidin, a specific constituent of raw egg white, was found to antagonize the carcinogenetic action of biotin, by rendering it nonabsorbable from the alimentary tract. It is 4,000 to 7,000 times as strong as raw egg white (Williams et al., 1941). Kaplan and Zurrow (1943) gave seven hopeless cancer patients the dried white of three dozen eggs a day, the equivalent of 1/7 grain of avidin, and obtained a striking reduction of the cancer in some. They report in detail cases of cancer of the tongue and cervix. Williams (1943) reports a sixty-six year old man, who lived for a long time on two to six dozen raw eggs a week in wine, and little else, but he developed cancer. Rhoads et al., (1942) were unable to demonstrate any relation of biotin to ordinary cancer development, and on the administration of avidin, observed no limitation of cancer growth.

Rhoads et al. have found that in stomach cancer the ability of the body to store and distribute *vitamin A* is seriously impaired, and this state continues even when enormous doses of A are administered. In 88 per cent of patients with cancer of the gastro-intestinal tract or of the head of the pancreas, or bone sarcoma, the blood levels of vitamin A were below normal. In leukemia, they found similar disturbances in the utilization of *thiamine.*

Vitamins and Infections.—Animals with marked vitamin A

deficiency may show snuffles, pharyngitis and bronchitis. In colleges, in children's wards, and in industry there have been many comparative studies on the value of administered vitamins in reducing the incidence of *upper respiratory diseases*, or in reducing the severity and duration of attacks. In most instances vitamin A has been the vitamin of choice, but thiamine, riboflavin, nicotinic acid and vitamins C and D have also been tried out. While some reports have been favorable, most have shown no especial benefits from continued high dosage. In some instances cod liver oil seems to have had a beneficial influence when vitamin A has failed. It has been suggested that only

Aids in the Recognition of Early Vitamin Deficiencies[1]

Vitamin	Signs	Symptoms	Accessory Laboratory Data
A	Xerosis conjunctivae, hyperkeratosis	Night blindness	Decrease in plasma A level
C	Gingival hypertrophy, anemia	Spongy bleeding gums, painful joints, subcutaneous hemorrhages	Roentgen changes in long bones, decrease in plasma C level, response to saturation test, capillary fragility
Niacin	Stomatitis, glossitis, cheilosis, papillary atrophy, nonspecific perineal lesions, urethritis, vaginitis, pellagrous dermatitis, depression, reactive psychosis	Nervousness, anorexia, diarrhea, sore mouth and tongue, epigastric burning	Decrease in urinary excretion of niacin
Riboflavin	Magenta glossitis, cheilosis; seborrhea; nasolabial folds, ears, forehead	Eyes: lacrimation, photophobia, discharge; sore tongue and mouth	Vascularization of cornea, decreased urinary excretion of riboflavin
Thiamine	Central ophthalmoplegia, symmetrical polyneuropathy, combined system syndromes, cardiovascular disturbances	Weakness, fatigability, paresthesias —burning, calf tenderness, edema	Nerve degeneration as shown by biopsy, decrease in urinary thiamine excretion
K	Hemorrhages, with disorders of absorption or jaundice	Bleeding	Increased prothrombin time, other evidence of hepatic disease

[1] David Cayer, M.D., J.A.M.A., Nov. 9, 1946, p. 559.

when the diet is not adequate in vitamins does increased resistance to infection result from their administration. This would call for mixed vitamins. Clausen states that the normal antibodies of the serum and the power to produce antibodies are not affected by dietary deficiencies.

In *tuberculosis* cod liver oil has long been a favorite remedy. In many cases a deficiency in vitamin A has been noted, and Koerner (1941) found a progressive depletion of vitamins A and C as the disease progressed. McConkey and Smith reported that sputum-fed guinea pigs were not protected from intestinal tuberculosis by cod liver oil. But McConkey (1941) reported that of 437 patients at Raybrook on the regular diet forty-seven showed frank intestinal infection, while of 399 given 3 ounces of tomato or citrus fruit juice and one-half ounce of cod liver oil at each meal only three developed outspoken intestinal tuberculosis. In giving cod liver oil in large quantities, Norris and Church found it necessary to increase the B factors to prevent degenerative changes in the tissues and a lowered secretion of fat in the milk. Ralli et al. (1941) report considerable depletion of liver A and carotene in various acute and chronic infections.

For severe mixed vitamin deficiencies Jolliffe (1945) advises daily: A 50,000 units, thiamine hydrochloride 20 mg., riboflavin 10 mg., niacinamide 300 mg., ascorbic acid 300 mg.; for moderate deficiencies half these amounts.

VITAMIN PREPARATIONS OF THE U.S.P.

I. Simple.

Ascorbic acid (Vitamin C) and *Tablets*. Dose 50 mg. ($\frac{3}{4}$ gr.)
Menadione (Vitamin K) and *Tablets*. Dose, 1 mg. (1/60 gr.)
Menadione Sodium Bisulfite and *Injection*. Intramuscular dose 2 mg. (1/30 gr.)
Nicotinic Acid (Niacin) and *Tablets*. Dose, 25 mg. ($\frac{3}{8}$ gr.)
Nicotinamide (niacinamide) *Injection* and *Tablets*. Dose, 25 mg. ($\frac{3}{8}$ gr.)
Riboflavin (Vitamin B_2), *Injection* and *Tablets*. Dose, 5 mg. (1/12 gr.)
Thiamine Hydrochloride (Vitamin B_1), *Injection* and *Tablets*. Dose, 5 mg. (1/12 gr.)

II. Compound.

Rice Polishings (B complex, Tikitiki) and *Extract* (1 cc. equals 145 Gm. of polishings). Dose of extract, 8 cc. (2 drachms).

Dried yeast (saccharomyces siccum) and *Tablets*. A dose of 10 Gm. ($2\frac{1}{2}$ drachms) contains thiamine 1.2 mg., riboflavin 0.4 mg., nicotinic acid 2.5 mg.

Cod Liver Oil (oleum morrhuae), the partly destearinated fixed oil obtained from fresh livers of the codfish and other species of the family Gadidae (haddock, hake, ling, pollock, etc.), which are taken with the cod. Its vitamins are almost wholly held in an unsaponifiable portion which constitutes about 1 per cent of the oil. Cod liver oil contains not less than 850 units of vitamin A and 85 units of vitamin D in each Gm. It also contains 4 to 13 parts per million of iodine and 1 to 5 parts of arsenic. It should be kept in amber or dark, well-filled bottles, in a cool place, otherwise it loses A. The dose is 8 cc. (2 drachms). The *emulsion* is 50 per cent.

Non-destearinated Cod Liver Oil, the raw oil which contains much stearin and will congeal or deposit stearin on chilling. This oil is not for consumption, but is official to permit its importation for refinement in the U. S. To prevent the loss of vitamin A by oxidation, the oil is destearinated in this country in an atmosphere of carbon dioxide or nitrogen.

Halibut Liver Oil (oleum hippoglossi) and *Capsules*, not less than 60,000 U.S.P. units of vitamin A and 600 U.S.P. units of vitamin D in 1 Gm., dose 0.1 cc. (1½ minims).

Oleovitamin A and *Capsules*, 50,000 to 65,000 units of vitamin A and not more than 1000 units of vitamin D in 1 Gm., dose 0.1 cc. (1½ minims).

Oleovitamin A and D and *Capsules*, 850 to 1100 units of A and 85 to 110 units of D_2 or D_3 in 1 Gm., dose 8 cc. (2 drachms). An artificial cod liver oil which, if made with a vegetable oil, avoids the fishy taste.

Oleovitamin A and D Concentrated and *Capsules*, 50,000 to 65,000 units of vitamin A and 10,000 to 13,000 units of vitamin D in 1 Gm., dose 0.1 cc. (1½ minims). This is similar to Halibut Liver Oil with Viosterol.

Synthetic Oleovitamin D, either vitamin D_2 (Viosterol) or vitamin D_3 in an edible vegetable oil, 10,000 units of D in 1 Gm., dose 0.1 cc. (1½ minims). It is practically tasteless.

Hexavitamin Capsules and Tablets, vitamin A 5000 units, vitamin D 400 units, ascorbic acid 75 mg., thiamine hydrochloride 2 mg., riboflavin 3 mg., and nicotinamide 20 mg.

Triasyn B Capsules and *Tablets*, thiamine hydrochloride 2 mg., riboflavin 3 mg., and nicotinamide 20 mg.

The U.S.P. issues *Reference Standards* prepared under the direction of its Vitamin Advisory Board for distribution to research laboratories and manufacturers, as follows: Cod liver oil A, cod liver oil D, cod liver oil D for poultry food, ascorbic acid, nicotinic acid, riboflavin, thiamine hydrochloride, menadione, calcium pantothenate and pyridoxine hydrochloride.

Some cod liver oils, of which only a limited supply is available.

are much richer in vitamins than the minimum allowed by the Pharmacopoeia. Viosterol is usually given in solution in a vegetable oil, but its solution in propylene glycol makes it miscible with water or milk. A number of other fish liver oils, such as those of the shark, mackerel, swordfish, white sea bass and tuna, are much richer in vitamins than cod liver oil, and the relative amounts of vitamins A and D vary greatly from those of cod liver oil. Halibut oil has a low proportion of vitamin D and is often fortified with viosterol. The percomorphs are high in vitamin D.

The vitamins are classed in two groups, the *Fat Soluble*, vitamins A,D,E and K, and the *Water Soluble*, which include the vitamin B components and vitamin C. The former may be lost in the feces, especially in conditions of steatorrhea, or when much calcium changes the fats of the food into soaps which are unabsorbable. The water-soluble, because of their solubility, may be lost in the urine and sweat, or by the bowels in diarrhea, or in the cooking water if this is thrown away. In storage, freezing, drying (dehydration), canning, and cooking there is more or less loss of vitamins, sometimes quite extensive. When baking soda is added in the cooking vitamins B and C are destroyed.

The water soluble vitamins are not stored to any extent in the body and must be replenished more often than the others. The fat soluble ones are stored, chiefly in the liver, and, unless there is liver disease, will keep one going for a long time. However, a moderate deficiency of any vitamin below the minimal requirement may continue for a long period before recognizable symptoms develop.

THE FAT SOLUBLE VITAMINS

VITAMIN A

Vitamin A ($C_{20}H_{29}OH$) is an aliphatic primary alcohol which permits esterification. It is absorbed as a bile acid compound, and stored in the liver as a compound of fatty acid. It occurs in animal fats and oils, such as milk fat, butter, cheese and egg yolk, and is especially abundant in certain fish liver oils. Distinctions have been made between A_1, which is found in the livers of salt water fish and land animals, and A_2 from fresh water fish. In vegetables there is no vitamin A, but it is represented by its precursor, *carotene*, which is changed to vitamin A in the liver. Vitamin A is fairly stable, but in the presence of air it is readily oxidized by prolonged heat, light, irradiation, free fatty acids, rancidity or agitation. In canning, steps are taken to exclude air from the cans. Destearination of cod liver oil is now done in the U. S. in an atmosphere of nitrogen or carbon dioxide. By the older and cruder processes as much as 25 per cent of the vitamin A was lost by oxidation.

Vitamin A is essential for normal *growth* and *nutrition*, for the development of the *teeth*, for the supply of *visual purple in the eye*, and for the integrity of the *epithelial tissues of skin and mucous membranes*. In its absence the skin shows roughness and dryness from stratified keratinization in the hair and sebaceous follicles, and brittle nails, and there may be keratinization of the epithelium of the eyes (xerophthalmia) with conjunctivitis and keratitis, of the respiratory tract with bronchitis or sinusitis, of the gastrointestinal tract, and of the genitourinary tract. A pronounced and early effect of A deficiency is night blindness (hemeralopia) in which there is loss of acuity of vision, with inability to see objects in subdued light or to adapt the eyes to dim light after a bright light. This is due to a deficiency of rhodopsin (visual purple), which is a protein compound of vitamin A. Aviators and airplane watchers have been treated with large doses of vitamin A for night blindness, and some have shown recovery and some not. It has been determined that other deficiencies, and psychic factors, without deficiency in vitamin A, may produce temporary night-blindness (Wittkower, 1941).

By giving four times the amount of vitamin A necessary for normal life and reproduction, Sherman, one of our greatest authorities on nutrition, has produced a super-race of rats. Their full adult capacity is reached earlier and retained longer, a period that in man would represent ten years.

Vitamin A counteracts thyroxin, and excess of thyroxin, as in hyperthyroidism, causes depletion in the stores of vitamin A (Clausen, 1938). In vitamin A depletion the vaginal mucous membrane of rats becomes cornified, but in vitamin A excess rats had no estrus cycle and no desire to copulate. Fasold (1937) gave 145,000 units of vitamin A daily for seven months to seven menstruating adolescent girls with large goiters, and four failed to menstruate until after the vitamin was stopped. Vitamin A has been used with success in senile vaginitis.

In animals deficient in vitamin A, Higgins, (1936) reported deposition of phosphate and carbonate *stones in the kidney pelvis*, and their solution under vitamin A administration. The stones were attributed to effects on the renal pelvic epithelium. Ezickson and Feldman (1937), Long and Pyrah (1939) have reported pathological dark adaptation in many cases of urolithiasis, but no improvement under high doses of vitamin A, while Jewett et al. (1943) found vitamin A deficiency in only one of ninety-eight cases of urolithiasis.

Carotene (pro-vitamin A, $C_{40}H_{56}$) exists in alpha, beta and gamma forms, and as the closely related pigment, cryptoxanthin. The beta is the prevalent form and is highly potent. It is a yellow colloidal pigment soluble in oil but not in water. It is more vulnerable than vitamin A to heat and oxidation. Its absorption probably depends

on the formation of a compound with bile salts. Some of that in food is lost in the feces, at times a considerable amount. Most of that absorbed is converted in the liver to vitamin A by an enzyme, carotenase, but some escapes into the blood in noncolloidal form and may be deposited in fat tissues. In liver disease, especially cirrhosis, the change to vitamin A may fail. When abnormal amounts are ingested, as in eating raw carrots to excess, or when there is a low rate of conversion to vitamin A as in diabetes and liver disease, *carotenemia* may develop, the skin turning yellow. This is distinguishable from jaundice as it shows excessively in the palms and soles, and not in the eyeballs and soft palate. The author has seen three marked cases. Carotene occurs in green, orange and yellow vegetables and fruits, such as asparagus, carrots, yellow corn, lettuce, Hubbard squash, spinach, sweet potatoes, tomato, green peas and beans, and apricots, bananas, oranges and peaches. Milk and butter contain both vitamin A and carotene, usually in the ratio of 1:1 to 2:1. In contrast with vitamin A, it has more affinity for mineral oil than for the lipids of the intestinal fluids, and, on the administration of this unabsorbable oil, may be carried from the body and lost. (See "Mineral Oil.")

Vitamin D

Occurrence.—There are ten or eleven known substances with the properties of vitamin D, probably six of them occurring in cod and other fish liver oils. Only two are used in medicine, vitamin D_2, artificially made by the activation of ergosterol, a vegetable substance, or related bodies, and vitamin D_3, present in animal fats and the fish liver oils; or made by the activation of 7-dehydrocholesterol. Vitamin D_2, or *calciferol*, is crystalline and is represented by viosterol and allied substances. It is less active than vitamin D_3, which is that formed naturally in the animal body through the action of the ultraviolet rays of the sun on the 7-dehydrocholesterol which is present in skin, fur and feathers. For medicinal purposes vitamin D_3 is supplied by the action of sunlight or the ultraviolet rays on the skin, by activated 7-dehydrocholesterol, by ingested fish liver oils, and to a slight extent by foods, such as milk, butter, cheese, eggs and the fatter fishes. Fresh milk in summer contains 20 to 27 units of D in a liter (quart); butter, 80 units, and the yolk of egg, 390 units in 100 grams. The only preparations containing vitamin D without vitamin A are the artificial preparations made by the activation of ergosterol and of 7-dehydrocholesterol. By over-irradiation ergosterol changes to a toxic substance, *toxiferol.*

In addition to the above as suppliers of vitamin D are various irradiated foods. *Vitamin D Milk* is of three kinds: (a) *Irradiated D Milk*, 135 units of D_3 in one liter. (b) *Metabolized D Milk*, 400 units of D_2 in one liter, obtained by feeding irradiated yeast to the cow.

(c) *Fortified D Milk*, of which one liter holds 400 units of vitamins D_2 or D_3, depending on whether the milk is fortified by viosterol or by fish liver oils.

Action.—Vitamin D is known as a *bone calcifying, antirachitic* and *antitetanic agent* of great potency. Its action is essentially *to promote absorption of calcium and phosphorus* from the intestines, to lessen their re-excretion into the intestines, and to normalize the proportions of these in the blood. The result in growing children is to promote normal deposition in the metaphyses of the bones and in the teeth. Its value would seem to be solely its effect on the calcium and phosphorus. It increases the rate of metabolism and the power of the blood to carry calcium. In the blood in jaundice it shortens the coagulation time (Ivy).

Toxicity.—Different effects reported from massive doses in *animals* are hypercalcemia, hypercalcified bones, hemorrhagic gastritis, nephritis or nephrosis, and calcium deposits in kidneys, lungs and the arterial walls. In rats and mice, daily large doses for a long time have resulted in gastro-intestinal disturbances, malnutrition, kidney changes and vascular calcification. In young rats daily doses of 25,000 units of vitamin D inhibited the normal calcification of the bone matrix, and raised the capacity of the blood to hold calcium rather than that of the bones (Ham and Lewis).

In *humans*, enormous doses, 200,000 to 600,000 International Units, have been given daily for many months without any signs of toxicity. A number, however, have developed one or more of the following: Nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, disturbed muscular coordination, aching muscles, weakness, frequency of urination and polydipsia. In a large series of rheumatoid arthritis cases given hundreds of thousands of units daily, Snyder and Squires (1941) noted untoward symptoms very infrequently and these were very mild. Danowski et al. (1945) report two cases of renal damage, in one of which there was extensive calcification of the soft tissues. Freeman et al. (1946) also noted two cases of renal injury. Bauer and Freyburg (1946) report a death in an adult due to metastatic calcification in arteries, heart and kidneys, and call attention to at least five others. Several deaths have occurred in children.

In fifteen of 200 infants Gordon and Lieberman noted loss of appetite and weight, vomiting, diarrhea and colic. On the other hand, in several hundred children given several times the usual dose for long periods, Schelling and Johnson observed no toxic effects, and, in thirteen who died, autopsy showed superior calcification at the bone ends but no changes in the other tissues. In one tuberculous child there was calcification in the peribronchial lymph nodes and the tuberculous tissue.

Therapeutics.—The great value of the fish oils lies, not in their fat, but rather in their high content of vitamins A and D. Even the minimum requirement cod liver oil has a vastly greater vitamin value than butter. These vitamins are of special value in winter, when sunlight is low and foods are low in vitamins. Less refined cod liver oil given to poultry improves the vitamin of the egg. Viosterol and other activated materials represent vitamin D alone.

Rickets.—This condition, very common in infants, is due essentially to a deficiency of vitamin D, and it has become the practice to administer cod liver oil or viosterol to all infants and young children. Cod liver oil is given the preference, and it may be that the vitamin A is a contributory factor in the prevention and cure. Viosterol is less efficient in equal unit dosage. DeSanctis and Craig reported that of 100 infants given 12 cc. of cod liver oil a day only three developed rickets, while Mitchell and Coley found that 8 to 12 cc. a day protected only 82 per cent, and viosterol, in doses giving double the amount of vitamin D, protected only 75 per cent.

As a prophylactic, Park (1940) starts with 2 cc. (30 minims) of cod liver oil daily at the beginning of the third week, increases this to 4 cc. (1 drachm) after a few days, and then in two weeks gives 8 cc. (2 drachms), which he continues through the first and second years. To premature infants he gives 1,000 to 10,000 units of vitamin D a day. In established rickets, Park finds that 1200 units in cod liver oil daily bring most patients into the curative stage in three weeks. Vollmer (1940) advocates a single dose of 600,000 units hypodermically in an oil and ether medium, the calcification line appearing in three to seven days. Frick (1941) prefers 7.5 mg. of crystallized calciferol twice a day. In *acute tetany* Park gives in addition 3 to 4 Gm. of calcium chloride at once and 1 Gm. four times a day for two or three days.

When rickets is being treated, success is indicated by a line of calcification crossing the transparent cartilage just beyond the end of the shaft of the long bones, as shown by x-rays. As the infant is usually born with poor reserves of vitamin D, cod liver oil is often given in pregnancy, a helpful procedure to some extent. It is also given to nursing mothers to improve the milk. Jeans and Stearns figure that an infant on cow's milk requires in addition 300 to 400 units of vitamin D a day. Only concentrated oils should be employed for young infants that do not swallow well, since lipoid pneumonia has been caused by the inhalation of particles of cod liver oil. *Osteomalacia,* which suggests rickets but occurs only after the growth period is ended, is treated in the same way as rickets.

Ultraviolet rays have proved useful in the prevention and cure of rickets. They require to be used carefully until the skin is tanned to protect the dermis from inflammation. The rays are absorbed by the

7-dehydrocholesterol of the skin. In spite of the heavy pigment, radiation cures rickets in the Negro. *Sunshine* and *skyshine* are valuable in summer, but in winter they are almost useless. At Toronto it was estimated that exposure to the sun at noon for twenty minutes in June was equal to an exposure of three or four hours in January. In the tropics rickets occurs because the mothers keep their infants entirely out of the sun on account of its intensity. Sunlight contains about 1 per cent of ultraviolet or actinic rays. Window glass removes all the ultraviolet rays of sunlight, but not the light and heat rays.

Rheumatism, Rheumatoid Arthritis.—Dreyer and Reed reported good results from the use of vitamin D in massive doses. With the administration of 200,000 to 600,000 U.S.P. units daily for an indefinite time, Livingston noted decided improvement in from one week to two months in many chronic arthritics, though several showed toxic symptoms. Wyatt et al. gave 200,000 U.S.P. units a day to forty patients with proliferative arthritis, and in eight there was clear-cut improvement, in 24 no definite benefit, and in eight such toxic manifestations that the drug had to be stopped. Slocum (1942) of the Mayo Clinic, reported a 25 to 75 per cent reduction of the symptoms in seven of fourteen patients. All these authors found no effect on the red or white blood cells, and practically none on the calcium and phosphorus of the blood; but there was a decrease in the sedimentation rate, and, in Schilling's test, a shift toward the right.

The approval by physicians of the very large doses in rheumatoid arthritis is by no means universal. Tumulty and Howard (1942), McChesney and Messer (1942), warn against large doses as hypercalcemic and toxic to the renal tubules with persistent kidney impairment. (See Toxicity p. 73.)

In Infected Wounds.—Cod liver oil has been used as a local application in burns, wounds, sluggish ulcers, diabetic gangrene, and peripheral vascular disease, in the colon in ulcerative colitis, and as a spray in *tuberculous laryngitis and pharyngitis*. It is claimed that the oil is itself sterile; that it is bacteriostatic and bactericidal; that it liquefies necrotic material, and that it stimulates granulation and epithelization. Aldrich (1942), of Harvard considers a 70 per cent ointment as good as the sulfa drugs. Other reports vary in their enthusiasm for its use. The Council on Pharmacy and Chemistry could find no evidence that any good effects are due to the vitamins present.

In addition, cod liver oil, or the pure vitamin D of activated substances, is used in *tuberculosis*, in *pregnancy* and *lactation*, in *tooth caries*, in conjunction with other vitamins and calcium, and in any form of *calcium and phosphorus imbalance*, as *osteoporosis* and *osteomalacia*. Favorable reports also are received of the value of

vitamin D in doses of 200,000 to 400,000 units a day in *hay fever, acne* and *psoriasis*.

VITAMIN E

This vitamin occurs in greatest abundance in wheat germ oil; is found also in the germs of other seeds, and in minute quantities in seed oils such as cottonseed, and in many foods. Chemically, it has been synthesized as *alpha, beta and gamma tocopherol,* the alpha form being the most active. It is readily oxidized on exposure to air, but is fairly resistant to heat. In the body it is stored in fat and muscle.

It appears to be necessary for reproduction and the placental functions, and is called the *reproductive vitamin,* because its deficiency results in degenerative changes in the gonads of both sexes. In the male, the spermatogenetic cells are destroyed, and complete and incurable sterility results unless treatment with vitamin E is begun while some of the tubules are still intact (Sherman and Smith). In the female, sterility results, but the destructive effects are temporary and may be overcome. Colonies of animals may grow normally and appear healthy yet fail to reproduce. With a single dose of 3 mg. of alpha-tocopherol, Evans and Burr restored the regular production of normal litters in female rats that had failed to reproduce while on a vitamin E deficient diet. In pregnancy, because of interference with the placental functions, there may be abortion, stillbirth, or eventual resorption of the fetus.

It seems to be necessary for the *integrity of voluntary muscle,* its lack resulting in spastic paralysis or muscular dystrophy.

It has been used in cases of sterility and habitual abortion, and in amyotrophic lateral sclerosis and muscular dystrophies and atrophies, but there is little evidence of its value. Of 128 cases of the toxemia of pregnancy Shute (1946) reports 92 per cent going to full term. The dose of the wheat germ oil is 1 to 4 cc. (15 to 60 minims). That of alpha-tocopherol is 500 mg. in oil. No preparation is official.

Vitamin K is Menadione, discussed elsewhere.

THE WATER SOLUBLE VITAMINS

Vitamins B and C are water soluble.

THE VITAMIN B GROUP

Twelve or more components of vitamin B are known. They are found in rice polishings and yeast. The ones of most interest for humans are thiamine, riboflavin, and nicotinic acid, but of some importance also are pyridoxine, pantothenic acid, para-aminobenzoic acid, biotin, choline, and possibly inosotol. Thiamine, riboflavin, niacin, and some other members of the vitamin B group would seem to be dependent for their biological activity on the formation of a

coenzyme, cocarboxylase, phosphorylated, and united with a divalent metal such as magnesium, and with an amino acid.

Thiamine (Vitamin B_1)

This, the *antineuritic vitamin*, occurs in quantity in only a few foods, such as lean pork, oatmeal, whole wheat or enriched bread, whole seeds, peas, beans and peanuts. There are slight amounts in many vegetables and fruits, and in milk, cheese, eggs, liver and kidneys. It is crystalline, acid, hygroscopic, and soluble freely in water and in 100 parts of alcohol. A solution of 1 in 20 has a pH of about 3.5. In water-alcohol solutions, such as an elixir, it precipitates as thiochrome after a few months. It is stable if kept dry. In solution its stability is increased by acids, and it is decomposed by alkalies, as when sodium bicarbonate is added in cooking vegetables. It can be sterilized for an hour at 100° C. without loss of potency. It is partly destroyed in the body and stored but little, chiefly in the brain and slightly in liver, heart and kidneys. It is excreted by the kidneys, but in profuse sweating is lost in the sweat and, in watery diarrhea, in the feces. On account of the loss in the sweat, the Army is giving it to the troops in the tropics.

Thiamine has an important influence on the *metabolism of carbohydrates*, serving to promote the disposal of pyruvic acid and indirectly of lactic acid. In some cases of diabetes it has lessened the amount of insulin required. Its need is increased with the caloric intake, the estimated requirement being 0.5 mg. for 1000 calories. It is required in increased quantity in pregnancy, lactation, diarrheal diseases, fevers, continuous profuse sweating, hyperthyroidism, and the period of active growth.

A marked *deficiency of thiamine*, long continued, results in the disease, beriberi. In normal people, tested by a diet deficient in thiamine but adequate in all other respects, there have been noted: anorexia, absence of or low free gastric acid, abdominal distention, constipation: loss of weight; fatigue, nervousness, irritability, loss of memory, inability to concentrate; tachycardia, dilatation of the heart, dyspnea, and pains in the calf muscles and chest. In the electrocardiogram there is low voltage and a flattened T-wave. Pregnant women are prone to abort. The storage of glycogen in liver and muscle is decreased.

The effect of large doses of thiamine on appetite and the feeling of well-being is sometimes pronounced. In swimming, breath-holding and holding out the arms, McCormick found increased power from 5 mg. a day, and improved performance in the 100-yard swim from 50 mg. intravenously. It is important for the preservation of the appetite, and the avoidance of atonicity of the stomach and bowels, muscular weakness of the heart, mental instability, and polyneuritis.

In the thiamine deficient it improves the bowel functions, but in those with adequate thiamine added amounts are not laxative. It counteracts radiation sickness. It is essentially non-toxic. It is antagonistic to thyroxin. In leukemia, the body fails to utilize it (Rhoads et al., 1942).

The Nervous System.—In beriberi, alcoholic polyneuritis (see Alcohol), and neuritis from infection, pellagra, arsenic poisoning, anemia, and the vomiting of pregnancy, a shortage of B_1 is apparently the causative factor and calls for large doses subcutaneously or intravenously. The vitamin is reported helpful also in the spinal manifestations of pernicious anemia and the neuritis of arsenic and lead poisoning, in tic douloureux, and in local neuritis, as of the shoulder girdle or in sciatica, and for the eyes in methyl alcohol poisoning. Intraspinally, 50 mg. are used in tabes. Maurer and Tsai found partial depletion of B_1 detrimental to the higher nervous functions of rats, as measured by maze-learning ability.

Toxicity.—Reactions to its injection intravenously and intramuscularly are not uncommon, and its oral use is advised. Sudden death following an intravenous dose is reported, also pellagrous manifestations from repeated doses. Indeed, a large dosage of any of the individual members of the vitamin B complex alone, but especially of thiamine, is considered more harmful than beneficial, as it may lead to other vitamin B deficiencies. Therefore, an increase in one member of the complex should be accompanied by an increase in all.

Therapeutics.—Thiamine would seem to be indicated in all cases of malnutrition, but new clinical applications are being reported from time to time. It is required in abundance in (1) Anorexia. (2) Diarrhea. (3) Diuresis. (4) Alcohol, arsenic, or lead neuritis. (5) Pregnancy and lactation. (6) Radiation sickness.

Riboflavin (Vitamin B_2)

This vitamin is bitter, soluble in 9 parts of water and slightly in alcohol, and heat stable. Its aqueous solutions are fluorescent, and it is preserved by acid and destroyed by alkali and light. Its saturated aqueous solution has *p*H about 6. Its best sources are yeast, rice polishings, liver (pork, beef, calf), beef heart and kidneys. A fair amount occurs in lean beef, lean pork, eggs, milk, cheese, wheat germ, cereals, broccoli, carrots, green beans and peas, spinach, tomato, peanuts. Along with thiamine and nicotinic acid it plays a role in the utilization of carbohydrate, and it is necessary in the oxidation processes in cells. Combined with phosphoric acid and protein it forms an oxidation enzyme. It is absorbed from the intestines, and is stored to a considerable extent in the liver, and slightly in the kidney and

heart muscle. The daily required amount is difficult to obtain from food, except perhaps liver. It is excreted in urine and feces, and with other water soluble vitamins is lost with excessive excretion of water. It is made synthetically.

Notable in *mild deficiencies* are ulcers or fissures at the corners of the mouth (cheilosis), a scaly, greasy desquamation in the nasolabial folds, the alae nasi and the ears, and injected conjunctiva and sclera. The lips may be dry and red, with stomatitis and glossitis. The scalp and other parts of the skin may show seborrhea, and the scrotum and vulva a dry itching. The eyes may show, in addition, photophobia, lacrimation, visual fatigue, blurred vision and a vascular keratitis. Cataract has developed in animals. In 472 children, Spies et al. (1940) reported underweight, underdevelopment and apathy.

It is used when these conditions are present, and in the dermatitis of pellagra. Its administration produces a feeling of well-being. It is non-toxic.

Nicotinic Acid (Niacin)

Nicotinic Acid, U.S.P., the *anti-pellagra vitamin*, is a pyridine derivative, soluble in 60 parts of water and stable in air. It may be autoclaved. A 1 per cent aqueous solution has a *p*H about 3. *Nicotinamide, U.S.P* (niacinamide) is very soluble in water and alcohol. Its 1 per cent aqueous solution has *p*H about 6. Because of flushing of the face, neck and extremities, rapid heart, and sometimes nausea and vomiting when even as little as 30 mg. of nicotinic acid is administered, but not when nicotinamide is given, the latter is preferred where possible. Also on account of its solubility and its low acidity this is best suited for parenteral use.

Nicotinic acid is abundant in nature. Its best sources are beans, soy beans, peanuts, lean pork, liver, wheat germ, yeast, rice polishings and enriched white flour, but it also occurs in fair amount in nuts, eggs, whole wheat, rye, oatmeal, molasses, cabbage, spinach, bananas and other foods. It is absorbed from the alimentary tract and deposited in the liver. It forms part of a hydrogen transporting coenzyme, which is fundamental in fermentation, glycolysis and cell respiration.

A marked *deficiency* results in the dermatitis, stomatitis, glossitis, urethritis, proctitis, vulvitis, vaginitis, diarrhea and mental symptoms of pellagra, and there is prompt remission (Spies et al., 1940) from 500 mg. of nicotinic acid daily, given orally in ten divided doses. For complete cure thiamine and riboflavin are also necessary. Nicotinic acid also cures black tongue in dogs, and King (1940) reports rapid healing of Vincent's angina. It is also given in large doses in sulfa drug sickness, irradiation sickness, delirium tremens, arteriosclerotic encephalopathy, and multiple sclerosis. It is non-toxic.

OTHER B VITAMINS

Pyridoxine Hydrochloride, U.S.P. (Vitamin B_6) is a crystalline pyridine compound, soluble in 5 parts of water and 90 of alcohol. Its aqueous solution, at *p*H below 6, can be sterilized at 121° C. for twenty minutes. Its sources are liver, yeast, rice polishings, wheat germ, seeds, legumes, molasses, meat, fish and some other foods. It has shown value in agranulocytosis. In pernicious anemia, Spies et al. obtained a slight reticulocytosis, and its deficiency in adult dogs and pigs results in a microcytic, hypochromic anemia. McKibbin and Elvehjem (1942) found the blood calcium level low, and the blood plasma iron high, as distinguished from that in the red cells. Jolliffe observed good results in Parkinsonism from 50 to 100 mg. a day. It has also seemed of benefit in arsenical neuritis, Sydenham's chorea and pseudohypertrophic muscular dystrophy. In agranulocytosis due to arsenicals, sulfonamides and other drugs, 200 mg. intravenously daily, with or without 200 mg. by mouth, has resulted in a rapid increase in the granulocytes.

Pantothenic Acid is available only as the *calcium and sodium pantothenates. Calcium pantothenate, U.S.P.* is freely soluble in water and slightly in alcohol, is neutral or slightly alkaline, and is unstable in solution. It cannot be autoclaved. It is quickly destroyed in the body or excreted in the urine. Siegel et al. (1941) found 33.3 micrograms in 100 cc. of the blood of normal persons. Pantothenic acid is widely distributed in nature, its chief sources being liver, yeast, rice polishings, egg yolk, molasses, whole wheat, oats, rye, cereal seeds, peas, beans, peanuts, broccoli and yellow corn. Its deficiency in the rat results in poor growth, dermatitis, adrenal hemorrhage and graying hair. When deficient in female rats before mating, pregnancy failed or the litters were defective (Nelson and Evans, 1946). It is considered a necessity in pellagra. Much interest has developed in its possibilities as an "*anti-gray-hair* vitamin." It shares this action with para-aminobenzoic acid, biotin, and possibly inositol. It is non-toxic.

Para-aminobenzoic Acid, the pronounced antagonist of the sulfonamides (p. 644), has been dubbed the *chromotrichia factor* for rats, and its deficiency shares with those of pantothenic acid, biotin, and possibly inositol, in the graying of the rat's hair. Martin et al. (1941) showed that it modifies the formation of melanin, the hair pigment. Sieve (1941) gave it to thirty gray-haired persons, and the hair was darkened in all. In gray-haired prison inmates Ansbacher et al. (1942) restored the hair to the original color in two-thirds of the cases, by giving 100 mg. twice a day for eight months. In 1 Gm. daily doses intravenously its sodium salt is specific in rickettsial disease and in radiation sickness. Its 10 per cent solutions prevent sunburn.

***Choline**, closely related to the B vitamins,* is described on p. 56.

Biotin, a sulfur derivative of urea, is soluble in water, and is rendered unabsorbable from the alimentary tract by avidin, a principle of the raw white of egg. It is indispensable for life. Yeasts and bacteria require a lot of it, for example, the germs of erysipelas. It is suggested that in the alimentary tract some disease germs that need biotin will die if raw white of egg is administered. Young rats depleted of biotin immediately after weaning develop a seborrheic dermatitis and show a high mortality. Four volunteers on a low biotin allowance, under Sydenstricker et al., (1942) at two to four weeks developed a scaly desquamation with pruritus, and at seven to eight weeks a grayish pallor of skin and mucous membranes, a lowered hemoglobin and red cells, and a rise in the cholesterol of the blood. They were restored to normal by the administration of biotin. Trager (1943) found increased resistance to malaria in chicks and ducks. (See also Cancer and Vitamins.)

Inositol is called the *alopecia vitamin,* as its deficiency in animals is accompanied by falling of the hair. It also has to do with graying of the hair. In chicks, Elvehjem et al. (1941) could detect no symptoms from its deficiency other than inhibition of growth. It is a necessity for growth and health, and is thought to be a necessity in fat metabolism, but little is known about it.

Other B vitamins now undergoing investigation are **folic acid** (Elvehjem), and vitamin Bc, a crystalline product of liver, which has 500,000 times the antianemic power of fresh liver (Hogan et al., Pfiffner et al., 1946). See Folic Acid.

Ascorbic Acid (Vitamin C, Cevitamic Acid)

Ascorbic Acid, U.S.P., $C_6(H_8O_6)$, is crystalline and soluble in 3 parts of water and 30 of alcohol. It darkens on exposure to light, and in aqueous solution rapidly deteriorates in air. It is destroyed by oxygen and heat, and by alkalies, as when sodium bicarbonate is added in cooking vegetables. Its 1 per cent aqueous solution has *p*H about 2.7. It is levorotatory and is synthesized from sorbitol and other sugar relatives. It is a powerful reducing agent, quickly reducing silver nitrate and potassium permanganate.

Sources.—It is widely distributed in nature, and is especially abundant in the citrus fruits, tomato, the cabbage family (broccoli, brussels sprouts, cabbage, cauliflower, kohlrabi), peppers, beet greens and strawberries. Of fresh orange and lemon juice 100 cc. contain 65 to 130 mg., grape fruit juice about two-thirds as much, tomato juice one-third as much, and cow's milk 20 mg. in a liter. Daniel et al. of the Bureau of Home Economics find the highest concentration in navel orange juice, but in proportion to size the navel orange contains the least juice, so that in oranges of the same size the different varieties yield about equal quantities of the vitamin. The juice of the

early season is richer than that toward the end of the season (Lorenz.) In the animal body it is present in practically all the tissues, and most abundant in the adrenals, the pars intermedia of the pituitary, the thymus and the corpus luteum. The least amount is found in muscle and fat.

Elimination.—It is absorbed from the intestines and partly stored and partly utilized. An excess is excreted in the urine, but in its deficiency little or none appears in the urine. Its requirement may be tested by giving a large dose and estimating the return in the urine; if the body needs it little is recovered. It is also estimated by the amount in the blood, which is normally about 10 mg. in 100 cc. It is needed in increased quantities in *states of high metabolism* and *cellular proliferation*, as in fevers, hyperthyroidism, leukemia, pregnancy, lactation, tuberculosis, rheumatic fever and plumbism. It is lost in abnormal amounts in diuresis, watery diarrhea and profuse sweating. Bernstein (1937) found an average hourly loss of 2 mg. in the sweat of mine laborers. The Army is giving it daily to soldiers in the tropics.

Destructibility.—Of all the vitamins it is the most readily destroyed by sun drying, storage and cooking. In cooking some is lost if the cooking water is discarded. Orange juice in a refrigerator lost 10 per cent of its vitamin C in six hours, tomato juice 40 per cent in three or four days. At the end of three months cold storage citrus fruits may contain practically none. Milk loses by age, agitation, extreme cold, heat, light, and contact with metallic catalysts, as in copper vessels. In pasteurization 20 to 50 per cent may be lost, and infants fed on sterilized milk have developed scurvy.

Action.—Ascorbic acid takes part in oxidation-reduction reactions; it is a hydrogen transport agent between the metabolites and molecular oxygen. It regulates the maintenance and deposition of the non-epithelial intercellular cement substances, the collagen of fibrous tissues, capillary walls, cartilage, the matrix of bone, and the dentine of the teeth. But it does not change the capillary resistance, as formerly believed, a function now known to be governed by vitamin P. It increases the thrombocytes and the coagulability of the blood. *In the eye it lessens senile changes*, particularly the development of cataract. But a cataract once formed is not removed by its administration.

Therapeutics.—*Bones.*—Bier found the union of fractures hastened by the administration of fruit juices, and Israel and Frankel that a C deficiency slowed calcification and delayed fracture repair. Conn et al. found that inadequate amounts in the diet of a pregnant woman might lead to a debilitated fetus, and during lactation might result in poor bone and tooth development in the infant.

Gastro-Intestinal Tract.—In C deficiency, Eusterman and Mayo reported slowness in the healing of experimental lesions of the gastric

mucosa, Abderhalden frequent ulcers in guinea-pigs, and McConkey and Smith 26 per cent of guinea-pigs with ulcer. In peptic ulcer patients Syderhelm found diminished bleeding on feeding vitamin C. The low C may be due to the diet, for Davidson reports 3 cases of scurvy in patients on ulcer diets. By the injection of 150 mg. of cevitamic acid daily by vein, Hetenyi had good results in 6 of 7 patients with ulcerative colitis.

Scurvy results from a prolonged deficiency of vitamin C. It is characterized by: (1) Decalcification and loosening of the teeth (or in infants imperfect dentition), absorption of the alveolar processes, pyorrhea and bleeding gums. (2) Subperiosteal, subcutaneous and submucosal hemorrhages. (3) A microcytic or slightly macrocytic anemia from retarded maturation of the erythrocytes in the bone marrow. (4) Degeneration of the skeletal muscles. (5) Necrotic foci in the liver. The bleeding is due to changes in the consistency of the intercellular cement substance of the finer blood vessels and to reduction in the blood platelets. Scurvy is not uncommon in infants, especially those on pasteurized milk, and even in the United States appears more or less in adults. Subclinical or latent scurvy is believed to be not infrequent. The specific preventive or cure for scurvy is vitamin C, which may be administered as orange or lemon juice or as crystalline ascorbic acid.

Infections.—In thirty-seven guinea-pigs on a C deficient diet, though with added cod liver oil, Smith and McConkey found that swallowed tuberculous sputum was followed by intestinal tuberculosis in twenty-six while in thirty-five on the same diet supplemented with tomato juice only two developed intestinal tuberculosis. De Savitch and Radford had similar results. In forty-four pulmonary tuberculosis patients, Heise and Martin found the excretion of vitamin C inversely proportional to the tuberculosis activity, an indication that tuberculous patients require extra C. Animals on a C deficient diet, *i. e.*, with latent scurvy, show low resistance to streptococcus, staphylococcus aureus and pneumococcus. It is believed to promote wound healing, especially of fractures.

Administration.—Orange juice is the favorite, but ascorbic acid may be taken in capsule or tablet by mouth or given intramuscularly or intravenously. As the solution of ascorbic acid in water is very acid, a decinormal solution (1.76 per cent) having a *p*H of about 2.5, hypodermic doses are prone to cause local necrosis with the formation of a sterile abscess, and intravenous doses, hemolysis. It is quickly oxidized by air in the presence of alkali, but the irritant effects may be avoided by neutralizing to *p*H 7 just at the time of administration by the addition of half its weight of sodium bicarbonate (Leach). A 1 per cent solution in physiologic solution of sodium chloride or a 3 per cent solution in distilled water is practically iso-

tonic. Ampuls with the acid in partial neutralization to pH 6 must be used at once on opening.

Dosage.—The curative dose for infants with scurvy is 100 cc. of orange juice daily, or 50 mg. of ascorbic acid daily by mouth, intramuscularly, or intravenously. For adults several times these amounts are required. In severe cases ascorbic acid in a single massive dose may be administered intravenously. Infants have been given 400 mg. intravenously and adults 1500 mg., without harm. For milder C deficiency, fruit juices are adequate, but, if the stomach is sensitive to fruit, ascorbic acid or sodium ascorbate may be given in doses of 20 to 100 mg. three times a day by mouth.

Other Vitamins

Vitamin M, a water soluble factor found in *yeast* and *liver*, prevents the mouth lesions of pellagra in monkeys. Day et al. (1938) report that its deficiency results in lowered resistance of the gastrointestinal mucosa, so that gingivitis and colitis may result. Healthy carriers of *B dysenteriae Flexner* developed active dysentery when placed on a vitamin M deficient diet (Janota and Dack, 1939).

Vitamin P (Citrin) occurs in the peel and juices of citrus fruits and in paprika. It is crystalline, is sparingly soluble in water, and is excreted in the urine. It is a mixture of the glycosides hesperidin and eriodictyin. Its function is *to maintain the capillary resistance and permeability*, or to restore it, as in purpura and hemorrhage when the blood shows normal coagulability. It does not influence the concentration of fibrinogen, prothrombin or platelets in the blood, and is ineffective in mechanical purpura and thrombocytopenia. Good results have followed orange peel, orange and lemon juice, and oral doses of hesperidin, 1 Gm. a day. It would seem to be the factor that checks the hemorrhages in scurvy.

Rutin, a glycoside chemically related to vitamin P, and derived from buckwheat or tobacco, is slightly soluble in water, oral dose 60 to 180 mg. (1 to 3 gr.) daily. *It acts to lower capillary fragility. It has no effect on blood pressure.* But Griffith et al. (1946) in 1600 consecutive hypertension cases found increased capillary fragility in 18 per cent, and in these gave it to avoid retinal or cerebral hemorrhage. It is used: (1) To prevent vascular accidents in hypertension with fragility. (2) In hereditary hemorrhagic telangiectasia. (3) If fragility is present, in thiocyanate medication, persistent epistaxis, bleeding of the gums, pulmonary hemorrhage, hematuria, melena, and various purpuras, but not in thrombopenic purpura.

COUNTERIRRITANTS

These are remedies which, by irritation of the skin, are intended to counter or check deeper-lying affections. Several degrees of skin irritation may be produced, viz., *rubefacient*, or reddening, *vesicant*,

or vesicle producing, and *epispastic*, or blistering. Beyond this an irritant may produce death of tissue. There are a few drugs, such as mercuric chloride and croton oil, which attack the gland mouths and produce pustules (pustulant effect). In therapeutics, in almost all cases, it is desirable to confine the irritation to the rubefacient degree. If the application is too strong vesicles and blisters appear.

Blistering is very rarely employed as a remedial measure. For not only is the blister a painful lesion, requiring treatment of itself, but it effectually prevents further applications to the skin at that spot. Unintentional blistering frequently results because of neglect to remove a mustard poultice, or from an excessively hot application in conditions where the patient is devoid of feeling, as in transverse myelitis or coma. In brunets an area of blistering or even vesication may be followed by permanent pigmentation.

Action.—The *mode of action* of counterirritants has been the subject of much speculation, but the recognition in recent years of a relationship between the viscera and certain areas of the skin and body wall through the nervous system has thrown much light upon the matter. Dana (1887) called attention to "referred pains" as being due to the distribution of the nerves, and Head (1893) and Mackenzie (1902) determined that tenderness of the superficial tissues might be a manifestation of inflammation or injury of one of the internal organs. Recent physiologic studies have shown that pain is elicited only in structures supplied by the cerebrospinal nervous system, and that viscera supplied by sympathetic nerves have no proper pain sense. The apparent pain in inflamed viscera is thus due to a reflex effect through the cerebrospinal nerves. Hence in appendicitis, cholelithiasis, pulmonary tuberculosis, etc., the superficial tissues are sometimes so tender as almost to preclude examination. Hurst concluded that pain in disease of the alimentary tract may be situated in the skin, muscles and connective tissues, and Lemene, Roth, and others find that cocainization of the superficial tissues of the abdominal wall checks the pain from visceral lesions. Sherrington demonstrated that on cutting certain nerves passing to the intestines and stimulating the central cut ends, the abdominal muscles contract in a definite manner. Also, it is a well-known physiologic fact that pain tends to cause contraction of the splanchnic arteries.

These findings all go to show a very close relation, through the nervous system, between the tissues of the body wall and the contained viscera, and tend to explain how irritation of a superficial area may have a decided effect upon a deep-lying or even remote viscus which is in no way in direct connection or contact with the irritated area. In this way may be understood the expulsion of flatus by the intestines as the result of a turpentine stupe applied to the abdomen, though the intestines have no direct anatomical connection with the anterior abdominal wall; or the effect of a mustard foot

bath in pelvic congestion; or a of mustard paste on the chest in pleurisy or pneumonia.

As working theories, Head and Hurst adopt the *segmental* relation, *i. e.*, that a lesion affecting a nerve from a given segment of cord or brain affects all the nerves whose centers are in that same segment. "Head's areas," mapped out on the skin by Head as being the areas of tenderness in the various visceral affections, have not, however, been at all constant, and Mackenzie has pointed out that in visceral lesions pain and tenderness do not appear in the whole distribution of any one segment, but in limited areas in the distribution of two or several segments. Therefore, Mackenzie suggests a *regional* relation rather than a segmental one. The good action of reflexes from skin stimuli may be the result of a conferred hypersensitiveness to stimuli owing to the visceral inflammation, to reflex changes in the circulation, or to other so far unknown effects.

Rubbing the back will sometimes distinctly affect the viscera, which suggests a reason for the success, in some instances, of the osteopathic plan of manipulating the spine and its neighborhood. Oliver found that a mustard paste over the liver sent the blood pressure from 105 to 135. But Wood and Weisman find that irritation of the skin of the hand by a mustard bath just short of producing dermatitis does not materially increase the rate of blood flow in the hand, the skin redness being presumably not accompanied by a change in the caliber of the deep-lying arterioles.

That counterirritation may act in other ways is also possible, for it is well known to every one that pain in a sensitive place results in a diminished sense of pain in a less sensitive region. It is probable, also, that the psychic suggestive effect, as of a thermocautery, may at times be important.

In the treatment of muscular or other tissues in direct contact with the skin, changes in the local blood supply may account for the remedial effect. Lazarus-Barlow has shown that a muscle on the same side as a blister has a higher specific gravity than the corresponding muscle on the unblistered side. And Wechsberg has demonstrated that when abscesses were experimentally produced in rabbit's legs, they were less extensive and healed more rapidly on the side to which counterirritants were applied.

Heat and Cold.—From heat applied to a limb Pemberton obtained muscular relaxation, hyperemia, increased capillary permeablity and local sweating. The minute flow of blood in the arm in an arm bath per 100 cc. of tissue Sprunt found to be 5.5 cc. at 26° C., 13 cc. at 32° C. and 26 cc. at 46° C., that is, the arteries were relaxed. From the application of heat or cold to the abdomen several experimenters have found no important change in temperature of the underlying viscera. In a woman with a gastric fistula, Dobreff observed the

interior of the stomach; an ice-bag to the abdomen caused hyperemia, and increased peristalsis and secretion, while a hot-water bag produced just the opposite effect. In a human intestine, Krogh obtained hyperemia from heat (46° C.) to the abdomen. Muller and Kast (1929) found that heat to the body surface decreased gastric and liver functions, while cold did the reverse. Bisgard et al. (1942) determined that heat to the abdomen inhibited the motor activity of stomach, small intestine and colon, without effect on gastric secretion, and that cold caused a sharp rise in both the motor activity and gastric secretion. Sleeth and Van Liere (1937) found the emptying time of the stomach increased by heat and decreased by cold. Uspensky (1938) found just the opposite. Eberhard (1940) found that in the fasting stomach ingested ice water delayed the emptying time, but in the food-containing stomach hastened it.

Silbert (1942) reported that in blocked circulation of the legs with gangrene heat makes the pain worse by increasing metabolism and the need for more blood, while cold relieves. Eberhard (1940) found that of twenty normal subjects given ice water twelve showed reversed T in leads II and III of the electrocardiogram. In hemorrhage from the stomach, Stoker (1939) found that heat accelerated the production of blood coagulant factors, while cold does the reverse. Hammet et al. (1929) found that heat to the abdomen caused a rise in blood pressure, presumably from constriction of the splanchnic arteries, while cold produced no change. Blalock and Mason (1941) report that in shock from hemorrhage and trauma the application of heat throws an added burden on the circulation and lessens the chance of survival.

Thus, the evidence would indicate that the ice bag used in gastric hemorrhage and appendicitis should be replaced by heat, and the hot applications to the legs in arterial disease and to the body in shock should be replaced by cold, or perhaps lukewarm.

From 250 cc. of ingested ice water at 40° F., Eberhard (1940) observed a drop of 30 to 60 in the intragastric temperature. Gershon-Cohen et al. (1940), after a similar cold drink found that it took thirty to forty-five minutes for return to normal, and after a hot drink at 145° to 165° F., fifteen to twenty minutes.

From a hot poultice on the chest wall, Leonard Hill reports a decided rise in the intrapleural temperature. From applications to the head 13 degrees above the body temperature, Macleod and Taylor obtained a rise of 2.7° F. in the animal brain; and from applications 45 degrees below the body temperature, a fall of 5.9° F. This corresponds with Sherrington's observations on the effect of an ice-cap. With an ice-bag over the precordium, Gilman and White obtained a fall in blood pressure in thirteen of twenty-five cases, and a rise in five, while the pulse rate was slightly slowed in nineteen. With a

large hot application over chest and abdomen, Roth obtained a rise in blood pressure of about 8 mm. in each of two patients. Mudd and Grant find that chilling of the body causes vasoconstriction and ischemia in the nasopharyngeal mucous membranes, and Sprunt found that cold to the surface might result in internal vasodilation.

While heat and cold cannot be transmitted through the abdominal wall, they may be passed through the chest wall and skull, though what influence this may have is not known. Reflexly they may affect the functions of organs and may relieve pain.

Summary.—The good effects of counterirritation may be due to: (1) a segmental or regional nervous relation between superficial tissues and the viscera. (2) The countering effect of a superficial pain over a deep-seated one. (3) A direct circulatory effect. (4) A psychic effect. (5) A reflex effect on the functions of the viscera and their blood supply.

COUNTERIRRITANT MEASURES

The more commonly employed counterirritant measures are: heat, cold, dry cupping, and drugs.

Heat is applied as an electric pad, a hot-water bottle, a hot stone or flatiron wrapped in cloth, or a poultice when the desire is to apply something that will keep hot a long time, or for a short time by an electric lamp, diathermy, or the high-frequency current. For a sudden application of heat the stupe or thermocautery may be employed. A *stupe* is a towel wrung out of very hot water; a turpentine stupe is made by sprinkling 1 cc. (15 minims) of oil of turpentine on the hot towel. In the use of the *thermocautery* for counterirritant effect the skin should not be seared, but merely reddened by the rapid passage over it of the red-hot iron or platinum point. *Poultices* may be made of linseed meal, bread, flour, bran or hops boiled with water and wrapped in cheesecloth or any thin fabric. The clay poultice, a proprietary name for which is "antiphlogistine," has kaolin and glycerin as its basis, with added small amounts of boric acid, oil of peppermint, methyl salicylate, and thymol. It has practically no absorption power for water, but acts essentially by its heat (Roth); so for use it is heated in its container and smeared over the part with a knife or stick. Roth showed that it had less power as a counterirritant and retained heat for a shorter time than a flaxseed poultice.

Cold is for the most part secured by an ice-bag or ice-water coil. Continuously applied it has more effect as a systemic antipyretic than as a counterirritant. Fauntleroy believes that in some cases of appendicitis the ice-bag is responsible for poor walling off of the lesion and poor resistance on the part of the patient, as shown by the failure of the leukocytes to increase much above the normal. Dobreff's experiments suggest the inadvisability of its use in gastric hemorrhage. (See also Antipyretics.)

Dry cupping is a process of suction applied to the skin by means of specially made cups or small tumblers in which a vacuum is created by swabbing out the cup with a cotton probe dipped in alcohol and then lighting the alcohol, or igniting some cotton stuck in the bottom of the cup. The cup must be instantly applied; and in order that it may hold and perform its suction, its application must be in a region where the tissues are soft enough to be drawn upon. Care should be taken not to burn the patient and not to leave the cups long in one place. Dry cupping is not now much employed because of its awkwardness, but in extreme cases, as in edema of the lungs or suppression of urine, may be resorted to. (*Wet cupping*, by cutting the skin and then cupping to remove blood and serum, is no longer employed.)

Drugs.—These are all, in the nature of the case, general protoplasmic irritants. The rubefacients are: *camphor, menthol* and *chloral hydrate*, any two of which solids, when mixed together, become liquefied; the *liniment of camphor and soap, chloroform liniment, alcohol, methyl salicylate, oil of turpentine, tincture of iodine, ammonia water, capsicum*, and *mustard* (*allyl isothiocyanate*). The N.F. recognizes *turpentine liniment* and *acetic turpentine liniment* (Stokes' liniment), the latter made into an emulsion with egg and water.

Mustard U.S.P. (sinapis) is the ground seed of black mustard (*sinapis nigra*). Also *U.S.P.* is *mustard plaster.* (*Allyl isothiocyanate* (volatile oil of mustard) is N.F.) Its use depends upon the development of an irritant volatile oil when the mustard flour is mixed with water. (See Glycosides, Part I.) It may be employed in tho form of a mustard leaf (charta sinapis) dipped in tepid water, or as a thin mustard paste made by wetting a mixture of mustard and flour with tepid water and wrapping in cheesecloth. For an adult the paste may be made of one part of mustard to two or three of flour, according to the sensitiveness of the skin; for a child, one part to four or five of flour. A mustard paste usually reddens sufficiently in ten to thirty minutes, and its effect must be watched to prevent blistering. As soon as the skin is thoroughly reddened the mustard should be removed. Sometimes, with the idea of preventing blistering, white of egg or vinegar is mixed with the paste, or petrolatum is smeared over the skin at the site of application. Whether or not such measures are efficacious we are unable to say. In pelvic congestion with suppressed menstruation a mustard foot bath is sometimes employed. It is made by adding a tablespoonful of mustard to 4 quarts of *warm* water. A mustard bath for infants is prepared of half this strength. In all mustard preparations very hot water should not be used, as this destroys or retards the activity of the enzyme which forms the irritant volatile oil. The enzyme is destroyed at 60° C. (140° F.). It is to be borne in mind that the "hotness" of a mustard bath should be entirely due to

the mustard oil developed, and not to its temperature as recorded by the thermometer. Cases of poisoning by mustard give the symptoms of volatile oil poisoning, together with marked local inflammation in mouth, esophagus, and stomach. (See Carminatives.)

Cantharides (cantharis), not *U.S.P.*, is the dried and powdered brilliant green beetle, *Cantharis vesicatoria*, or Spanish fly. Its active constituent is 0.6 per cent of cantharidin, an acid anhydride which forms soluble salts with alkalis. The "fly blister" is a piece of adhesive plaster spread with *cantharides cerate*. About its only employment is in large inflammatory collections of fluid in the knee joint, as in acute rheumatism. A fly blister about 2 inches in diameter is applied to the skin for twenty minutes, then removed, and replaced by a flaxseed poultice. A large amount of serum collects beneath the skin and is removed by pricking the skin.

From its use to produce abortion, and its administration with the fancied purpose of stimulating sexual feeling, many poisoning cases have resulted. It is a violent irritant, the symptoms following large or undiluted doses being local irritation in mouth, esophagus, stomach and intestines, resulting in inflammation, blistering or ulceration, with vomiting, diarrhea, bloody stools and cramps. The kidneys and bladder also show intense inflammation, with bloody urine or suppression of the urine. There is sometimes priapism. Pregnant women may abort. The patient may go into profound collapse, resulting in death. The treatment is symptomatic, demulcents being administered by mouth and rectum, and collapse treated as described later.

Therapeutics of Counterirritants

1. *To relieve pain*—muscular, neuralgic and joint pains, as well as those associated with visceral affections (pleurisy, cardiac pain, biliary and intestinal colic and dysmenorrhea).

2. *To lessen abdominal cramps, inflammation* or *flatulency*.

3. *To relieve congestion and inflammation*—as in the case of inflamed lymph nodes, pelvic congestion and pneumonia.

4. *To promote absorption*—as of serous effusions in the pleural or peritoneal cavities or joints, in hydrocele, and in brusies or hematomata.

5. *To overcome tympanites*—as in the use of the stupe in typhoid fever or postoperative intestinal paralysis.

6. *To overcome collapse*—as in the use of mustard bath or alternating hot and cold plunges for infants.

7. *To check nosebleed*—ice to the back of the neck.

8. *To relieve cerebral congestion*—as the ice-bag in headache, delirium, meningitis, etc., or the menthol pencil in headache.

9. *To relieve hiccough*—over the nape of the neck and the diaphragm region.

Cautions.—Debility and old age, in which conditions irritants of all kinds tend to be depressing.

WAR GASES

The possibilities of war demanded a knowledge of the war gases and how to treat their effects. Following the schedule of Dr. Harry M. Rose (1942), they are:

Lung Irritants.—*Phosgene* is the most effective lung irritant, even in low concentrations. Following exposure there is either a completely latent period of one to twelve hours, followed by a deep blue cyanosis, intense dyspnea, and pulmonary edema, which may be fatal; or the subject goes into shock, with pallid cyanosis. *Chlorpicrin* may cause uncontrollable coughing, sneezing and vomiting, but is not fatal. *Chlorine* is no longer used.

Vesicants.—*Mustard gas* is really a volatile oily liquid. Not only does it severely damage the respiratory apparatus, but in addition it exerts a vesicant or blistering effect upon all epithelium. Within one to twelve hours there are cough, conjunctivitis with edema of the eyelids, and erythema of the affected skin, with severe itching. In severe cases there may be pulmonary edema with ulceration and necrosis of the tracheobronchial mucous membrane, and later, bronchopneumonia, lung abscess or empyema. From the ingestion of contaminated material there may be nausea and vomiting. Persons whose clothing is contaminated are a source of danger to others. The mortality rate is low, but rarely there is permanent blindness, pulmonary dysfunction or cicatricial contractures. It does not predispose to pulmonary tuberculosis.

Lewisite may produce arsenical poisoning, as well as pulmonary injury and severe burns of the skin. There are immediate tingling or smarting of the skin, burning of the eyes and respiratory irritation. The skin lesions, very painful vesicles not surrounded by erythema, show in fifteen to thirty minutes and reach their maximum in about twelve hours. The lesions penetrate into the underlying tissues. There may be permanent blindness.

Ethyldichlorarsene is weakly vesicant, but is a lung irritant and an arsenical toxic agent.

Lachrimators.—Exposure to low concentrations produces lachrimation and blepharospasm, which temporarily incapacitates, but leaves no serious after effects.

Sternutators.—These provoke violent sneezing, coughing and vomiting, which prevent the wearing of a gas mask as protection

against other gases used simultaneously. They also induce violent frontal headache, vertigo, pains in the limbs and joints, and extreme weakness. The effects disappear quickly.

Smokes are also used, such as *sulfur trioxide, titanium tetrachloride* and *white phosphorus.* For the last, cloths wet with copper sulfate are applied, and the burns treated. Incendiaries are *white phosphorus* and *thermit* ($8\,Al + 3Fe_3O_4$) and require the treatment for severe burns.

Preventive Measures.—The gas mask contains activated charcoal and certain chemicals, but is ineffective against ammonia, carbon monoxide and sulfur dioxide. Most of the gases are heavier than air, so it is advised to keep two floors above the ground and to close the windows. To be fully clothed gives the best protection, but some gases penetrate fabrics. Both mustard and lewisite can be carried through clothing, and an exposed person is a danger to others.

Treatment.—With *mustard gas* any liquid present on the skin is removed by clean cloths *without rubbing.* Then the skin is patted gently with cloths moistened with kerosene, gasoline, alcohol or carbon tetrachloride; washed with soap and water and patted dry with towels. The cloths and towels must be burned. The eyes are irrigated with physiological salt solution, and an anesthetic ointment applied, but not on any account cocaine. Nasal and throat irrigations and gastric lavage may be indicated. For *lewisite* the skin should be swabbed with hydrogen peroxide, or 10 per cent sodium hydroxide in 30 per cent glycerin, or, in lieu of these, a solution of sodium bicarbonate. The eyes must be cared for with 2 per cent sodium bicarbonate. Livingston, 1940, states that ascorbic acid intravenously is the best remedy for the eyes. The British have developed an effective antidote, BAL. (See Arsenic.)

The vesicles of mustard gas contain a nonirritating fluid, those from lewisite contain an irritant fluid and arsenic, and must be opened and drained. In pulmonary damage oxygen is indicated, and in the phosgene cases with blue cyanosis, venesection. Treatment for shock may be necessary.

CAUSTICS (ESCHAROTICS)

These are substances which act by causing the death of tissue. They may destroy by consuming the tissue, as in the case of sulfuric acid, or by precipitating protoplasm, as by phenol, or by causing an inflammation which results in a slough, as in the case of arsenic. The caustics are:

1. *Acids.*—Sulfuric, nitric, glacial acetic, trichloracetic.
2. *Alkalis.*—The hydroxides of potassium, sodium and calcium (lime).

3. *Metallic salts.*—Silver nitrate (lunar caustic), copper sulfate (bluestone), zinc chloride, burnt alum, chromium trioxide (chromic acid), arsenic trioxide (arsenous acid).

4. *Carbon dioxide,* liquid or solid.

5. *Phenol.*

There are also a number of caustic substances, such as mercuric bichloride, which are not used as such in therapeutics.

Sulfuric acid chars, *nitric acid* changes the part to yellow, and all acids act by abstracting water and neutralizing the alkalinity of the tissues. They are direct irritants, even when diluted. The *alkalis* abstract water and saponify the fatty substances of protoplasm; they are very penetrating, and make ulcers which are slow to heal.

Chromium trioxide (chromic acid) comes in the form of deliquescent, dark reddish crystals, which decompose or explode on the addition of glycerin, alcohol or other organic substances. *Potassium bichromate* is an irritant poison. Among chromate workers perforation of the nasal septum is the rule, and deep ulcers of the hands known as "chrome holes" and dermatitis may appear. They may be avoided by protection from the dust.

Toxicology.—When caustic acids or alkalis are swallowed, they burn and denude the tissues of mouth, esophagus and stomach, and produce shock. To neutralize acids, mild, noncarbonated alkalis may be used, such as diluted lime or magnesia; the carbonated alkalis set free too much gas. To neutralize alkalis, vinegar and lemon juice are good. For the burns, demulcents, such as olive oil, lard, white of egg, milk, etc., are indicated. (For poisoning by metallic salts and phenol, see later.)

Therapeutics.—*Silver nitrate, chromium trioxide* and *trichloracetic acid* are employed to remove exuberant granulations, small polypi, warts and hypertrophied soft tissues, as in the nose, and for large canker sores in the mouth. *Copper sulfate* is used for the eyelids. Caustics are now very little employed except for application to small and superficial areas. *Carbon dioxide,* in liquid or solid form, has been used to remove nevi, and in the treatment of lupus, sluggish ulcers, epitheliomata and leprosy.

To *cauterize* is to sear the tissues. It may be done with the thermocautery, or electric cautery, or by nitric acid, phenol (carbolic acid) or lunar caustic. Phenol is adapted for infected cavities or sinuses, the area being afterward washed with alcohol to check further penetration of the phenol. For dog bites, Bartholow, of the New York Department of Health, recommends the following in the order of their merit, viz.: (1) fuming nitric acid; (2) silver nitrate; (3) the actual cautery. The employment of the thermo- or electric cautery for the removal of tissue is quite different from its counterirritant use, in which the skin should not be seared.

THE DIGESTIVE FERMENTS

PEPSIN

Pepsin, N.F. is an enzyme usually obtained from the fresh mucous membrane of the hog's stomach. It is freely soluble with opalescence in water, but nearly insoluble in alcohol. It is destroyed by heat at 70° C. (158° F.), by strong acids, by 2.5 per cent solution of sodium chloride, and in the stomach by alkalis in amounts sufficient to render the gastric juice neutral. It is precipitated from solution by tannic acid and by the salts of many of the heavy metals. It acts in an acid medium of *p*H 1.3 to 4 to digest the proteins of the food. The optimum *p*H for digestion varies with the food; for example, it is 1.3 for egg albumin, 1.8 for casein and 2.2 for gelatin. At *p*H 5 pepsin is practically inert, so that to supply an effective artificial gastric juice that can be swallowed is a practical impossibility.

By the N.F. test, pepsin must be able to change 3000 to 3500 times its weight of coagulated egg albumin into soluble protein. In other words, 1 grain of pepsin can digest the protein of over 6 ounces of coagulated egg albumin. Northrup has isolated a crystalline pepsin seven times as powerful as this. Pepsin would therefore be a highly powerful therapeutic agent, were it not for the fact that it is a superfluous remedy. Extensive tests with human gastric juice have shown that, except in cases of achylia gastrica, the stomach rarely fails to secrete sufficient pepsin. Pepsin, with hydrochloric acid, is used topically to digest dead tissues and fibrinous membranes, and to produce experimental peptic ulcers in dogs. Pepsin regularly contains rennin, and will coagulate milk.

Preparations and Doses.—N.F.—*Pepsin,* 0.5 Gm. (8 grains); —*elixir,* 3.5 per cent, 8 cc. (2 drachms); *elixir of pepsin and bismuth,* 8 cc. (2 drachms); *glycerite,* 10 per cent, 2 cc. (30 minims); and others.

PANCREATIN

Pancreatin, (pancreatinum), U.S.P., is usually obtained from the fresh pancreas of the hog or ox. It contains the enzymes, trypsin, amylopsin, and steapsin. Ivy found *choline* in the form of lecithin, and Dragstedt *lipocaic,* which he considers a hormone, both of these acting to lessen fat deposits in the liver. Pancreatin acts best in a neutral or faintly alkaline medium, and is destroyed by the gastric juice, or by excess of alkali. Many investigators have found active trypsin in highly acid gastric contents, and Rehfuss et al. found it still active in contents with acidity 110, that had stood eighteen hours at room temperature. Of administered pancreatin, Long found the destruction less in the presence of food proteins and increased with the length of the exposure and the acidity. Aaron et al. found that by mouth it requires doses of at least 5 Gm. (75 gr.) on an